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BRAIN.

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MICROGLIA: AN EXPERIMENTAL STUDY BY MEANS OF TISSUE CULTURE AND VITAL STAINING.

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Introduction.

Recent progress in histological technique has advanced the knowledge of the cellular structure of the central nervous system, so that the adendritic cells of the brain are now known to be composed of two types of cells, the oligodendroglia and the microglia. In an exhaustive histological study of the microglial elements, Del Rio-Hortega [2] went far to demonstrate that microglial cells are of mesoblastic origin; this contention, however, has its opponents, amongst them being Metz and Spatz [11], who advanced evidence in favour of an ectodermal origin. While acknowledging the work of these histologists, it is apparent that until the origin of microglial cells is definitely established, false conceptions of the pathology of the central nervous system may arise.

The present paper records the results of some experiments performed in an attempt to elucidate the embryological element from which microglia arises. The problem has been attacked by means of tissue culture and vital staining *in vivo* and *in vitro*.

There appears to be comparatively little literature dealing with the cultivation of nervous tissue. In 1907 and 1908 Harrison [5] published his classical work on the development of excised portions of the nervous tissue of the frog after incubation in lymph removed from the lymph-sac. He was able to demonstrate the growth of a fibre from these cells which was in many ways similar to a neurone. More recently Mossa [12]

has shown that if isolated embryonic spinal root ganglia are incubated in a suitable medium, outgrowths take place which closely resemble nerve-fibres. None of these workers have, to our knowledge, attempted to recognize the cellular elements in their cultures by means of the selective silver impregnation methods of staining, and many of their conclusions must consequently be conjectural.

Material and Methods.

Material.—Cultures were made from the central nervous system of fowl embryos of from three to twenty-one days' incubation. Great care was necessary to rid the implant of overlying mesoblastic tissue and at the same time to avoid any considerable damage to the nervous tissue. Cultures showing outgrowths of fibroblastic tissue were immediately discarded. After repeated experiments it was found that the area of the pons and medulla was the most easily isolated. Dissection was carried out by means of needles and a binocular dissecting microscope.

Cultures were also made from periosteum, limb bud and retina for comparison with those derived from nervous tissue.

Culture technique.—Cultures were made in both solid and fluid media, by the usual coverslip technique [14]. Owing to the great delicacy of the retina, transplantation in solid medium was found to be impracticable. It was therefore grown in fluid medium only.

The solid medium employed was one drop of fowl embryo extract, diluted with Pannett's isotonic salt solution, mixed with one drop of fowl plasma. The cultures were changed to fresh medium every forty-eight hours.

The fluid medium consisted of the fluid expressed from the clot resulting from the addition of twenty drops of fowl plasma to thirty drops of embryo extract. One drop of this fluid was placed on the coverslip with the piece of tissue to be cultured, and the whole sealed off in the usual way. The culture was washed every forty-eight hours with embryo extract and a fresh drop of medium applied.

Vital staining technique.—In the experiments with vital staining *in vitro*, neutral-red and trypan-blue were used. The neutral-red was exhibited by substituting 0·5 c.c. of a 0·1 per cent. solution of neutral-red for 0·5 c.c. of distilled water in making up 25 c.c. of Pannett's solution. This fluid was used as a diluent for the embryo extract. In this dilution, about 1 in 100,000 in the final medium, no toxic effects upon the culture were observed. The trypan-blue was exhibited by substituting 2·5 c.c. of a 1 per cent. solution of trypan-blue for 2·5 c.c

of distilled water in making up 25 c.c. of Pannett's solution, giving a dilution of about 1 in 2,000.

The technique for the vital staining *in vivo* is given later.

Histological technique.—The cultures were placed in formol bromide, a 10 per cent. solution of formaldehyde (Merck's specific gravity 33) made up with 4 per cent. ammonium bromide solution. This solution was faintly acid. Fluids with a neutral or alkaline reaction to litmus were found less reliable. At the end of twenty-four hours in a second bath, they were placed in another bath of formol bromide and kept at a temperature of 37° C. for one hour. From this they were transferred without washing into a dish containing 25 c.c. of distilled water and two drops of ammonia, where they remained for a period of twenty to thirty minutes. From this, without washing, they were placed in a silver bath made up as follows: to 5 c.c. of a solution of 10 per cent. silver nitrate were added 20 c.c. of a 5 per cent. solution of sodium carbonate. Ammonia was then added drop by drop until the precipitate just disappeared, leaving a colourless and odourless fluid; 50 c.c. of distilled water were then added. The cultures were retained in this silver bath at a temperature of 37° C. for a period of not longer than fifteen minutes. They were then very rapidly washed in distilled water and placed in a bath of 1 per cent. formalin in distilled water: while in this bath the coverslips were kept on the move either by rocking or actually holding them in forceps and waving them to and fro in the bath. As soon as they ceased to cloud the bath or to become more brown they were transferred without washing into a bath of gold chloride (5 c.c. of a 1 per cent. solution of gold chloride to 25 c.c. of distilled water). In this they were left until the culture had become a dirty grey colour, when they were placed in a bath of 5 per cent. hyposulphite of soda. At the end of five minutes they were washed in several changes of distilled water, passed through the alcohols into xylol and mounted in Canada balsam. Several were also stained for fat with Scharlach R. and mounted in glycerine jelly. By these methods permanent specimens were obtained. As controls, frozen sections from adult tissue were found to stain admirably and selectively for microglia by these methods.

Microscopical Examination.

Histological appearances of tissues before explantation.—Pieces of the embryonic fowl brain chosen for cultivation were fixed, cut and stained by the method described. Blood-vessels were observed within the brain substance. This was of significance as showing the presence of meso-

blastic elements in the cultures. As this paper is not concerned with the other cells of the central nervous system, these will not be described.

Serial sections through the eye of the embryonic fowl were cut and stained by routine methods. Careful examination of the retina failed to reveal any blood-vessels within its substance. This fact was made use of in obtaining a pure culture of ectodermal tissue.

Observations on the living cells in vitro.—In the living brain cultures three main types of cells were seen: (1) A cell with a long process which grew out rapidly to cells already lying away from the implant; the processes from several such cells tended to become associated, and at their termination to spread out fanwise in very fine ultimate strands. (2) A small cell with an oval nucleus, having usually three, but occasionally two, cytoplasmic processes. Cells of this type were intermingled with those of the previous type at the plaque-like edge of the implant. (3) A round cell with an oval or slightly irregular nucleus. Cells of this form were distinguishable by the end of the first day's growth *in vitro*.

The present communication deals with the third type of cell only. The writers hope to discuss the possible nature of the other two types in a later paper.

The cell Type No. 3 was found in all cultures. It was actively motile, and in many cultures migrated a considerable distance from the implant edge. This was more marked when the culture medium was fluid. Further, in fluid medium these cells appeared to flatten themselves out on the coverslip, so that they had the appearance of being larger and of having a less dense nucleus than those in solid medium.

In cultures of three days' duration in solid medium, a definite change in the character of the cells was noted. They lost their round shape and became elongated and irregular in outline, whilst some protruded thick processes branching out in all directions. The nuclei at this stage were also elongated or irregular in shape.

Between the third and sixth days of cultivation *in vitro* more interesting changes were observed. The cells were seen to grow out into the medium in a series of chains, each cell being an independent unit and having the characteristics of the cells seen at the end of three days. During this period of growth mitotic figures were commonly seen. Towards the sixth day the cells tended to become more isolated, and there was less evidence of chain formation. At the same time, the cells ceased to be elongated and assumed an even more irregular shape with one or two long, fine processes passing centrifugally from the centre of

the culture. Cells of this type were present in the cultures up to the twenty-first day of cultivation.

After six days' growth some of these cells showed degenerative changes. These cells became rounder, with shorter processes, or in some cases with none at all. The protoplasm contained many small refractile granules, and the nucleus had become oval. Cultures in fluid medium showed more cells with degenerative changes than those in solid medium.

Observations were made by means of the dark-ground illumination method described by Strangeways and Canti [15]. Remarkable activity was observed in the cells. Protoplasmic protrusions were constantly thrown out and then withdrawn. Mitochondria and cell granules were in constant violent movement. Highly refractile fat droplets were present in varying amounts. The appearance and behaviour of the cells were exactly similar to those noted by Fell and Andrews [3] in the wandering cells of rat sarcoma.

Cultures of eight days' duration were chosen for vital staining. These were examined at frequent intervals under the microscope in a hot box at a temperature of 37° C. The neutral-red culture showed staining of the cell granules beginning about fifteen minutes after the commencement of cultivation. The granules were of varying size and scattered throughout the cell, but the largest number were seen round the nucleus. The staining increased in intensity up to forty-eight hours, when a maximum appeared to have been reached. The trypan-blue cultures did not show any dye in the cell for at least twenty-four hours after the commencement of cultivation. The granules of dye varied in size, but were smaller than the granules stained with neutral-red. They were scattered throughout the cell and were not especially congregated round the nucleus. The amount of dye in the cell increased up to ninety-six hours of cultivation.

In the cultures of periosteum and limb bud, cells entirely similar to those described were found. Their behaviour with vital dyes was strictly comparable.

The retinal cultures, whilst showing a good area of outgrowth, produced no cells of the Type 3 described in the brain cultures. The significance of this will be discussed later.

Observations on the cells after fixation.—The cells under consideration showed the typical staining reactions, after silver impregnation, which are seen in microglial cells. The nucleus had a fairly dense chromatin network. In cultures of three days' duration, or more, the

protoplasm had a dirty grey colour after silver impregnation, and there were a few dense black granules within the protoplasm. In places these minute dark granules appeared to be on the surface of the cell. The processes showed up well and closely resembled those seen in microglia from adult brain tissue.

The cells showing degenerative changes after six or more days' cultivation *in vitro* showed many small granules which stained well with Scharlach R.

The cells from the periosteum and limb bud cultures showed a very striking resemblance to those found in the brain cultures. Their form was entirely similar and they showed the typical staining reactions after silver impregnation.

Intravital staining experiments in vivo.—The literature on this subject is somewhat scanty, and the following is a review of the main works. Goldman [4], by using large intravenous doses of trypan-blue, was able to demonstrate a diffuse staining of the lepto-meninges: no certain staining of the neuroglial elements was observed. Woollard [16] injected the dye into the subarachnoid space and demonstrated the dye in the lepto-meninges and in the mesothelial cells lining the perivascular spaces which surrounded the entering vessels of the spinal cord and brain. In none of these experiments did the nerve, ependymal or neuroglial cells contain elements of dye. He repeated these experiments, adding laked blood-corpuscles to the trypan solution, so as to cause irritation of the lepto-meninges: the results in no way differed from those obtained in his previous experiments. MacCurdy and Evans [8] reported the staining of the glial nuclei and "Gitterzellen" in animals suffering from experimentally produced poliomyelitis or polio-encephalitis. After damaging the brain by puncture wounds, Macklin and Macklin [9] injected trypan-blue and demonstrated the presence of the dye in macrophages around the wound. More recently this work has been repeated by Russell [13], who has shown that the microglial cells in the vicinity of such a wound contain particles of trypan-blue: in the microglial cells situated farthest from the wound only one or two small granules were present, while in the active swollen microglial cells in the immediate vicinity of the wound there was considerably more dye. She assumed from this evidence that microglial cells were probably of mesodermal origin, as suggested by Del Rio-Hortega. Kubie [6], using the supravital technique, was able to stain the perivascular tissues of the central nervous system: but he was unable conclusively to demonstrate the presence of the dye within microglial cells. In a review of the

whole subject of vital staining, Capell [1] concludes that the dyes do not pass into brain tissue and are not taken up by any of the essential elements of the neuraxis except the lepto-meninges, choroid plexus and perivascular tissues. In spite of this apparent protection of the nervous tissues to vital dyes it was decided to carry out the following series of experiments.

Four rabbits were given intravenously a daily injection of 1 per cent. trypan-blue in distilled water. The injection varied from 5 to 10 c.c. At the end of ten days two rabbits, and at the end of fourteen days two others, were killed by ether anæsthesia. The brain was immediately dissected out and placed in formol-bromide. After two days hardening, frozen sections were made and stained by the method described at the beginning of this paper. Pieces of brain were also embedded in paraffin, cut and stained with a weak solution of carmine.

On microscopical examination the sections stained by means of the silver impregnation method proved of little value, as the colour produced by the silver staining and that of trypan-blue were impossible to separate. However, the microglial cells showed evidence of alteration from normal: the cells were larger, and had fewer fine processes. In other words, they resembled the stage when microglial cells are beginning to react in the neighbourhood of a wound. The sections stained with carmine were of considerable interest. In those rabbits which had received intravenous trypan-blue for a short period, there was a diffuse slight bluish tinge of the whole brain, but in the region of the hippocampus a more intense blue colour was present. Under the microscope the nerve-cells were found to have taken on a faint blue tinge: careful scrutiny failed to reveal granules of stain within the cell, and it was certain that the staining was not associated in particular with the Nissl bodies. The microglial cells that were approximated to the nerve-cells showed in more than one place the presence of blue pigment lying around the nucleus. The granules were small and difficult to observe unless care was taken. In the region of the hypothalamus microglial cells appeared to be more numerous and to contain blue granules. These microglial cells were situated in close proximity to blood-vessels. Their situation is of importance, as Kubie has shown that the monocytes in the region of the cerebral blood-vessels will take up neutral-red: it is, therefore, possible that these cells observed close to blood-vessels may have been monocytes derived from the vascular system.

In the brains of the rabbits that had been injected intravenously for a longer period, the presence of granules in microglial cells was strikingly seen.

To the naked eye the brains were stained a deep blue, especially in the region of Ammon's horn. Microscopically a large proportion of the cells which could be recognized as microglial were crowded with trypan-blue. Microglial cells which were satellites to neuronic cells were particularly rich in the dye : the dye was scattered throughout the fine processes of the cells, and at times was collected chiefly around the nucelus. This was especially noticeable in the regions of the basal ganglia, thalamus and Ammon's horn. The microglial cells in the cortex itself contained as a whole less dye, and many cells no dye at all. In the white matter throughout the brain many microglial cells lying away from any recognizable blood-vessel contained particles of the dye.

Scrutiny of the other nervous elements, such as the nerve-cells and neuroglial cells, failed to reveal the presence of particles of trypan-blue within their substance. However, cells in the perivascular tissues contained many particles, as did also the cells of the choroid plexus : the former cells are probably similar to the cells stained by neutral-red, as reported by Kubie.

From these experiments it was clear that microglial cells will take up particles of trypan-blue, provided the trypan-blue is supplied in sufficient quantities and concentration.

Discussion.

Cultures of embryonic brain have shown the presence of a cell which has many of the characteristics of microglial cells of adult tissue. This type of cell has the following resemblances to normal microglia :—

(1) A selective affinity for silver after the impregnation methods of Del Rio-Hortega.

(2) An irregular outline, with many processes, some of which are of the fine wire type.

(3) A nucleus of similar shape.

(4) Similar distribution of chromatin within the nucleus.

(5) The presence of fine dark granules in the protoplasm after silver impregnation.

We felt justified, therefore, in concluding that these cells were microglial cells.

The striking resemblance between the cells in the brain cultures and the wandering cells in the cultures of periosteum and limb bud suggested that these two types were identical. The wandering cells belong to the reticulo-endothelial system, and have been carefully described by Maximov [10], Lewis [7] and others. They are also known as histio-

PLATE I.

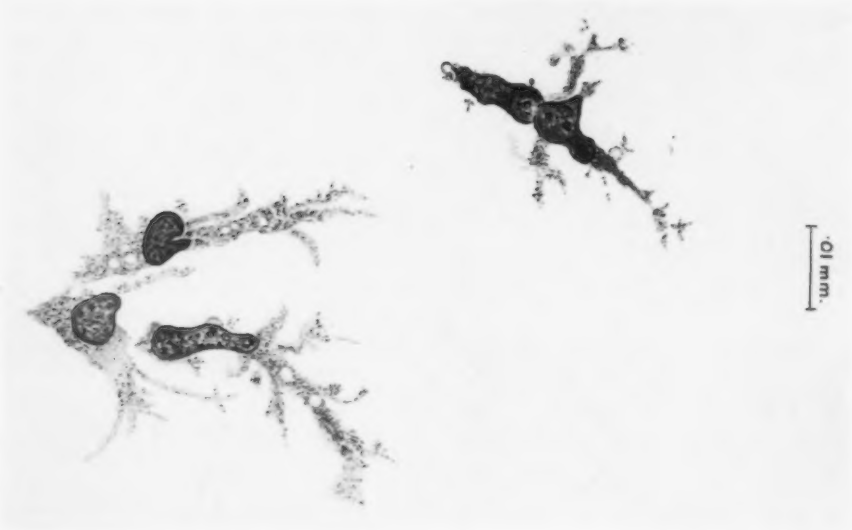


FIG. 1.

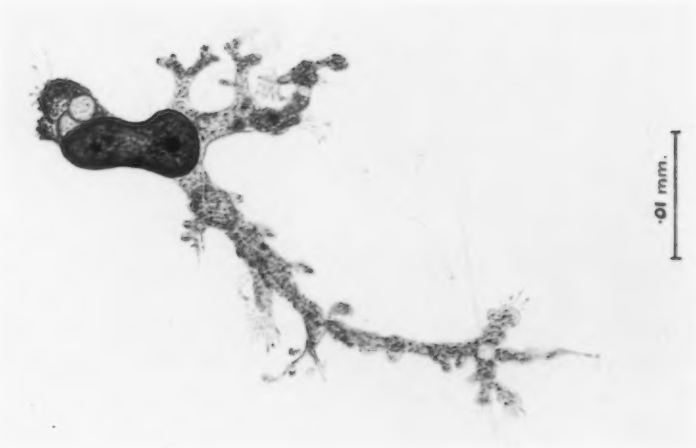


FIG. 2.

To illustrate paper by A. Q. Wells and E. Arnold Carmichael.

PLATE II.

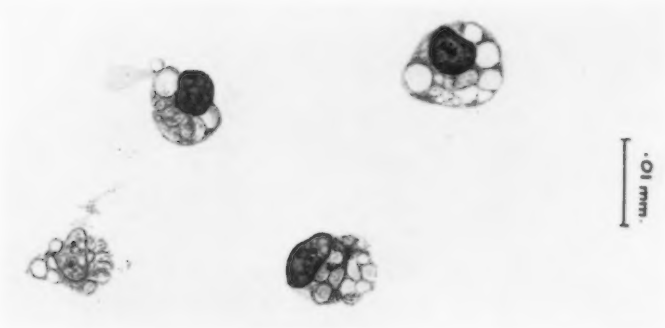


FIG. 3.

FIG. 4.

To illustrate paper by A. Q. Wells and E. Arnold Carmichael

PLATE III.

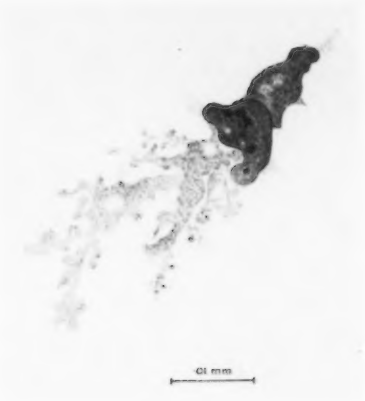
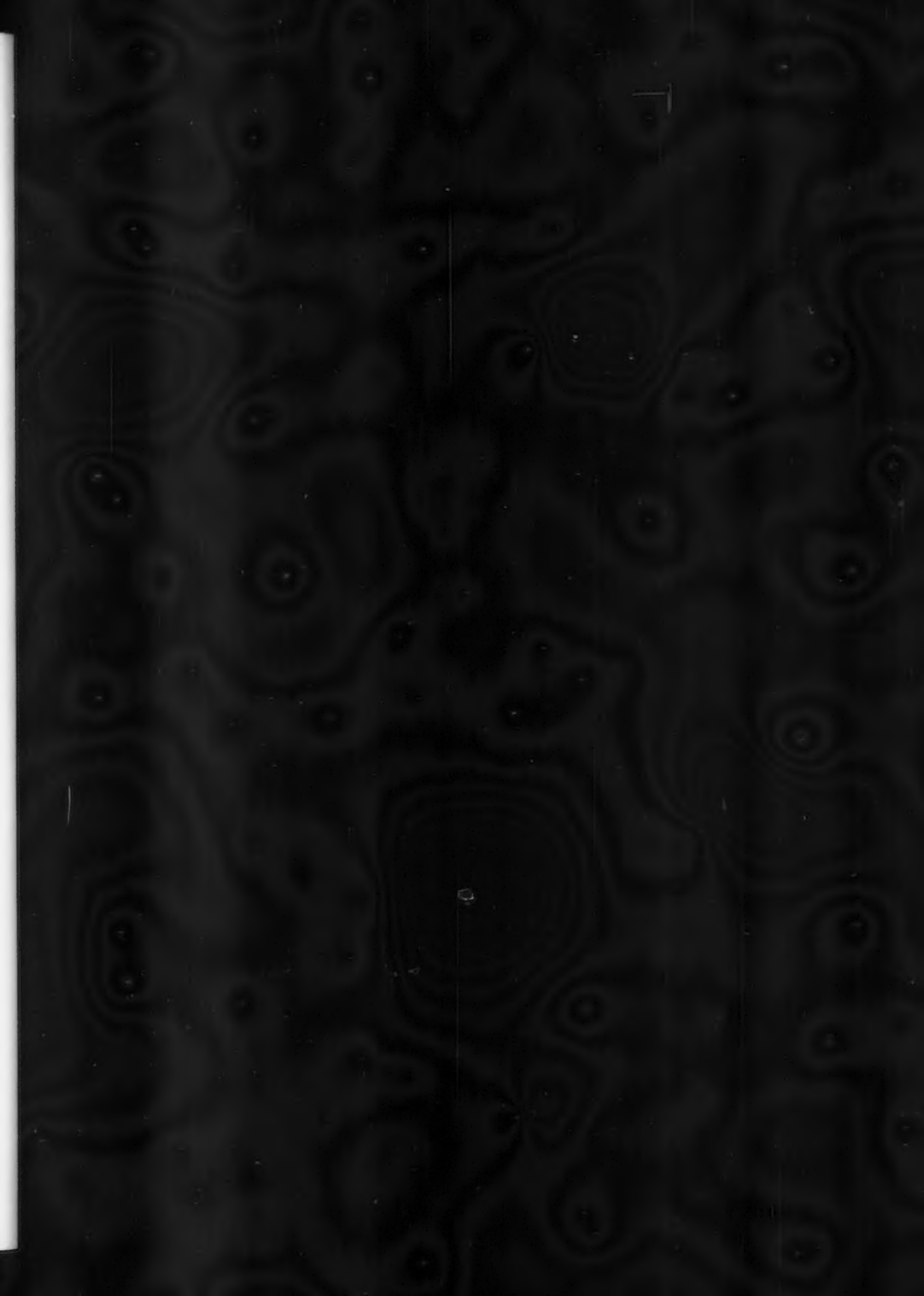


FIG. 5.

FIG. 6.

To illustrate paper by A. Q. Wells and E. Arnold Carmichael.



cytes and macrophages. They are of mesoblastic origin; they must arise from the blood-vessels, which, as has already been noted, were also present in the substance of the brain explanted.

The next step was to find some tissue that was definitely free from mesoblast. To obtain embryonic brain so early that blood-vessels had not formed, and at the same time to free it from the overlying mesoblast, was found to be impracticable. For this reason the purely ectodermal embryonic retina was used. As stated above, cultures from retina showed a complete absence of microglia-like cells. While recognizing that this was by no means a conclusive proof of the mesoblastic origin of microglia, it may be considered an additional fact in favour of such a conclusion.

The wandering cells of the reticulo-endothelial system have a definite affinity for the vital dyes. The series of experiments with neutral-red and trypan-blue showed that the cells cultivated from brain had the same affinity. The distribution of neutral-red within the cell was exactly similar to that described by other workers as occurring in wandering cells.

Finally, if it could be shown that normal microglia in adult brain also took up these vital dyes *in vivo*, the chain of evidence in favour of their mesoblastic origin seemed complete. As already described, experiments with trypan-blue *in vivo* showed that microglia has the faculty of ingesting the dye.

Conclusions.

1) Microglia is of mesoblastic origin, and is analogous to the resting histocytes or fixed macrophages of the reticulo-endothelial system.

(2) Microglia is probably a part of the reticulo-endothelial system.

Summary of Results.

(1) Fragments of brain from embryonic fowl of from three to twenty-one days' incubation were cultivated *in vitro* for from one to twenty-one days. These cultures showed cells closely resembling microglia.

(2) These cells showed characteristic staining with silver impregnation methods.

(3) Cultures from embryonic periosteum and limb bud showed exactly similar cells.

(4) Cultures from embryonic retina showed no such cells.

(5) These cells reacted to vital dyes *in vitro* in the same way as do wandering cells.

(6) Microglial cells showed phagocytic properties to trypan-blue *in vivo*.

It is a pleasure to us to express our thanks to Miss Fell, Director of the Strangeways Research Laboratory, for much help in practical details and for stimulating suggestions. We also wish to thank Professor Fraser for constant encouragement and helpful criticism. One of us (E.A.C.) carried out this work with the aid of a grant from the Medical Research Council.

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DESCRIPTION OF PLATES.

Fig. 1.—Cells from a culture of 16-day embryonic chick brain. Note the irregular-shaped nucleus and many branched processes. The resemblance to microglial cells of adult tissue is apparent.
Culture medium: Fowl plasma and embryo extract. 7 days' growth. Hortega impregnation method.

Fig. 2.—Cell from a culture of 16-day embryonic chick brain. The cell has an irregular-shaped nucleus and many branched processes and closely resembles a microglial cell of adult tissue.
Culture medium: Fowl plasma and embryo extract. 7 days' growth. Hortega impregnation method.

Fig. 3.—Cells from a culture of 5-day embryonic chick brain. These cells are round with irregular-shaped nucleus and contain globules of fat. They resemble the compound granular cells.
Culture medium: Fowl plasma and embryo extract. 18 days' growth. Hortega impregnation method.

Fig. 4.—Cells from a culture of 4-day embryonic chick periosteum. These cells have irregular-shaped nuclei and processes branched in varying degrees.
Culture medium: Fowl plasma and embryo extract. 21 days' growth. Hortega impregnation method.

Fig. 5.—Cell from a culture of 4-day embryonic chick periosteum. Note the irregular-shaped nucleus and many branched processes. This cell is very similar to an adult microglial cell.
Culture medium: Fowl plasma and embryo extract. 21 days' growth. Hortega impregnation method.

Fig. 6.—A drawing of microglial cells from the brain of a rabbit injected intravenously with trypan-blue. The upper three cells are from the region of the white matter; the lower cell is a satellite to a neuronic cell. Note the particles of trypan-blue in the processes and around the nucleus of the microglial cells.
Alum carmine stain.

SPINAL SYMPTOMS IN CHLOROMA AND LEUKÆMIA.

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In contradistinction to the cerebral manifestations of the severe disorders of the blood-forming organs, symptoms of a paraplegic kind have received comparatively scant attention in the literature. Although rarely mentioned, these spinal forms are not actually uncommon. Failure to recognize the importance of this association of neurological and constitutional symptoms has in part accounted for the incorrect diagnosis of the great majority during life. Again, the varied guise under which the paraplegia may appear has added to the difficulties.

Special problems arise in connection with certain of the spinal changes in the leucoses which, despite their rarity, may nevertheless throw light upon the causation of the commoner paraplegic manifestations of pernicious anæmia.

Among the contributions of note, certain stand out in importance. Such are to be found in Bassoe's article (1918) [1] and in Heissen's paper [13] on Chloroma and the Nervous System published in 1925. Two years later Holmes delivered an address to the meeting of the Association of Physicians, on the neurological aspects of leukæmia and chloroma, but his paper has never been published.

Some of the earliest references to the subject are of purely clinical nature and it is difficult to assign such cases to their correct category. Mosler's case [23] is illustrative of this point; in a very brief note he gives details of a clinical case of a man, aged 35, suffering from splenic anæmia accompanied by an interesting "tabetic paralysis" of the lower extremities.

Of more especial interest is the case recorded by Allan Burns [4] in 1824. In his "Treatise on the Surgical Anatomy of the Head and Neck," he gives a detailed account of what is probably the first recorded case of chloroma. A young man—the age is not stated—had noted for some three months a fullness in the superciliary region of the brow. Later the vision in the left eye became affected, followed a fortnight afterwards by diplopia, exophthalmos and ocular pain. The swelling

was incised but the pain persisted; the tumour increased in size and later sloughed. Other tumours developed—apparently arising from bone—and the right eye then began to bulge. Gradually the patient lost power in the legs as well as the capability of discharging his urine. Death concluded a state of extreme cachexia with decubitus. At the autopsy numerous greenish tumours were found in the lachrymal gland, the accessory nasal sinuses, the orbit, the surface of the skull bones and the dura; unfortunately the spine was not examined. Burns was, of course, unaware of the true nature of the disease, but gave an admirable discussion as to its probable type and also its relationship with fungus hæmatodes. "It presented none of the characters of that disease," Burns wrote: "the complaint seemed to me to have been one *sui generis* . . . how the disease was propagated, or what its nature was, are points on which we must confess our ignorance."

Another purely clinical case was recorded in 1917 by Schwab, Sale and Schmidt [35]. Their patient was a man aged 50, who experienced a sudden severe pain in the back. On the following day the legs were found to be weak, and in the course of the next three weeks they became totally paralysed and sphincter control was lost. Complete flaccid paraplegia was found on examination, with a sensory loss extending up to the fifth dorsal segment. A few days later signs of motor and sensory impairment appeared in the hands and arms, accompanied by difficulty in speech and swallowing. Enlargement of the liver and spleen was next demonstrated and hæmorrhages occurred in the skin. Blood examination revealed the leukæmic nature of the condition. The patient died sixty-four days after the onset of the symptoms. Post-mortem examination was not allowed.

In attempting to describe the various ways in which paraplegia may appear in association with leukæmia or chloroma, it will be advisable to adopt a classification based on pathology; to endeavour to deal with the problem according to the actual anatomical structures involved, and to specify the exact pathological variety of morbid process. For reasons already stated chloroma and the leukæmias will be treated together.

The paraplegic manifestations of these disorders will, therefore, be dealt with under the following seven heads:—

(1) Localized or diffuse leucocytic infiltration of the spinal cord.

(2) Localized or widespread softening of the spinal cord.

(3) Hæmorrhages into the spinal meninges.

(4) Infiltration of the spinal meninges by leucotic or chloromatous masses.

(5) Infiltration of the spinal nerve-roots.

(6) Infiltration of the peripheral nerves of the lower extremity.

(7) Manifestations of subacute combined degeneration of the spinal cord occurring in association with leukæmia.

(1) *Infiltration of the spinal cord* by aggregations of mature or immature leucocytes is not a common cause of paraplegia; it does not seem to occur in the chloromatous types. Such infiltration may be distributed diffusely throughout the substance of the cord or, on the other hand, may be collected into more localized leucoma nodules. The case recorded by Rosenstein [30] may be quoted in this connection.

Rosenstein (1881) described a case of leukæmia in a boy aged 7 who had been ill for some five weeks with enlarged glands and with general weakness. Examination of the nervous system revealed marked weakness of the legs with integrity of sensation. The knee-jerk was absent in one leg and barely obtainable in the other. The child was incontinent of urine. Post-mortem examination showed an infiltration in the lower dorsal and upper lumbar regions of the spinal cord with cells of the same type as were present in the visceral organs. The substantia centralis gelatinosa and the anterior and posterior commissures were the sites of maximum change. There was some dilatation of the central canal; the blood-vessels, including the finest terminal branches, were widely dilated, especially in the grey matter of the ventral horns. In general, the myelin and axis-cylinders were retained, although here and there they were lacking.

(2) Paraplegia may occur in the leucoses as the result of foci of *softening within the spinal parenchyma*. To this category belong the cases of Spitz [36] and of Baudouin and Parturier [2]. At various times such cases have been referred to as exhibiting areas of "myelitis"; detailed pathological studies make it clear, however, that the softened areas do not result from local inflammatory processes but are the secondary accompaniment of an affection of the spinal blood-vessels. Hypertrophy or hyaline degeneration of the vascular walls, particularly of the middle coat, predisposes to an accumulation of masses of leucocytes, and subsequent occlusion. In this way more or less extensive areas of myelomalacia are formed.

In 1901 Spitz referred to changes in the central nervous system in a fatal case of leukæmia. His patient had already been described clinically three years previously by Hirschlaff [14]. A woman aged 47 died from an acute leukæmia without showing any manifestations of

neurological disease. At the post-mortem examination numerous focal lesions in association with the smallest blood-vessels were found. These were present in some degree in the white matter of the cervical region of the spinal cord, but were most plentiful in the pons. Each focus comprised an accumulation of round cells mostly mononuclear in type. Some of the larger lesions showed central necrosis, and resembled caseating tubercles.

Baudouin and Parturier's patient was a male aged 64, whose history was one of three months intense pain in the back, extending upwards to the epigastrium and downwards to the legs. This symptom was accompanied by weakness. Three days before admission to hospital the legs suddenly became quite flaccid and helpless. He was found to have a complete paraplegia with abolition of all reflexes and retention of urine. The patient died six days later. At the autopsy it was discovered that he had extensive leukæmic deposits throughout the viscera; a post-mortem blood-examination revealed a large excess of myelocytes. The condition in the spinal cord was one of "subacute diffuse myelitis," most marked in the upper thoracic regions but also present at the cervical and lumbar levels.

In some of the recorded cases localized softenings may be present in addition to a more diffuse infiltrative process throughout the cord. This is exemplified in the case recorded by Bloch and Hirschfeld [3]. Their patient, a child of 8 months, died from myelogenous leukæmia. Examination of the nervous system after death revealed a peculiar hardness in the consistency of the brain and spinal cord; this proved to be due to a diffuse cellular infiltration of both grey and white matter; in addition there was a generalized neuroglial proliferation. At the level of the third and fourth cervical segments a focal softening was visible.

(3) The evidence that *meningeal hæmorrhage* in the spinal region may cause neurological symptoms referable to the lower extremities is confined, so far as we can trace, to a single case. In a patient described by Olivier [26] there were no paralytic signs in the strict sense, though severe cramps in the legs had been present for some time. His patient was an alcoholic male of 61, whose symptoms were those of enlarged glands, purpura, fits and delirium. The post-mortem examination showed a leukæmic infiltration of the liver. The meninges of the brain and cord contained numerous areas of hæmorrhage; in the latter situation they were especially numerous, and were located chiefly over the ventral aspect of the first thoracic segment, the dorsal surface of the

third segment and on the fifth thoracic segment. There was no compression of the spinal cord, as in every case a considerable space intervened between the hæmorrhagic plaques and the cord.

(4) The commonest cause of paraplegia in leukæmia results from a more or less extensive *cellular infiltration of the spinal meninges*. This is particularly common in chloroma, a disease in which there is a special tendency towards the formation of cellular masses, particularly in relation to the dura mater. Cell masses of this kind were present in the following four personally observed cases, but the supposition that they may have caused paraplegia by pressure is not altogether supported by the microscopical examination of the spinal cord in two of the cases.

Case 1.—G. F. Q., a male, aged 19, was on October 24, 1928, transferred to Dr. Critchley's care at the National Hospital, Queen Square, by Dr. J. B. Rolleston with a diagnosis of leukæmic paraplegia. The history was of three months' general malaise; during this period he had been subject to headaches and appeared paler than usual. Three weeks ago he awoke with a sudden pain in the back which radiated forwards; the legs were found to be numb and almost useless, and there was a difficulty in micturition amounting at times to an actual retention. Two weeks later his left eye became prominent, and two days afterwards he complained of some left-sided subcostal pain and vomiting. He was sent into the Western Hospital with the provisional diagnosis of typhoid. Here Dr. Rolleston found a condition of complete paraplegia. A blood-count showed 2,000,000 red cells and 136,000 white cells, of which a large proportion were myelocytes. The Widal reaction was negative.

Examination at the time of admission to the National Hospital revealed a very pale and emaciated man, completely paraplegic. Temperature 100·8° F., pulse 116, respirations 22. The mental state was normal. Both eyes were proptosed, especially the left; ophthalmoscopic examination showed that the disc edges were blurred; the blood-vessels were tortuous and engorged, and there were numerous hæmorrhages and areas of exudate. Lateral ocular movements were defective. No motor or sensory defect occurred in the upper extremities. Both legs were powerless except for very feeble attempts at flexion and extension at hip and knee joints. The tone was flaccid and there was some diffuse muscular atrophy. The abdominal muscles and the lower eight intercostals were paralysed. No form of sensory stimulus could be felt over the legs or trunk up to the fifth thoracic segment. There was a feeble knee and adductor jerk obtainable on both sides; otherwise all reflexes were in abeyance. There was lack of sphincter control with retention of urine.

The abdomen was distended and tympanitic: the liver was enlarged and the spleen was palpable a hand's breadth below the costal margin. Ecchymoses were present in the skin of the leg and thorax.

A blood-count gave the following result (Dr. Elizabeth O'Flynn):—

Red cells 1,270,000, Hb. 30, C.I. 1·2. White cells 229,000, polymorphs 50 per cent., myelocytes 41 per cent., hyaline 1 per cent., lymphocytes 5 per cent., transitional 2 per cent., eosinophils 1 per cent. Four megaloblasts were seen among 200 white cells.

Course.—The patient died on the fifth day after admission to hospital. During this period the temperature was constantly raised and varied from 99·6° to 103·8° F. He became weaker; delirium set in, and for the last twenty-four hours he was in a state of coma.

A post-mortem examination was carried out the next day by Dr. J. G. Greenfield.

Thorax.—The anterior surface of each rib was covered by a layer of green deposit which terminated abruptly at the costochondral junction. Similar material was found lying under the sternum and over the pericardium, where it seemed to have replaced the fatty remains of the thymus.

The *lungs* were somewhat nodular on palpation in their upper parts, but there was no evidence of tuberculosis nor any infiltration with chloromatous masses. A thin margin of collapse was found at the base of the right lung.

The *heart* was slightly enlarged. Some greenish streaks were seen under the epicardium along the line of the coronary arteries, and there were several cushion-like infiltrations on the right side of the interventricular septum. The right auricle and ventricle contained a very large greenish antemortem clot: the left ventricle a smaller one.

The *liver* was enlarged, weighing 2,680 grm. Numerous green infiltrations were seen on section along the lines of the portal vessels, and two large nodules of similar material were present on its anterior surface.

The *spleen* was large, congested and firm, weighing 250 grm.

The *kidneys* were swollen and pale, and the pelvis and perinephric fat of each was infiltrated with chloromatous material. The right kidney weighed 270 grm. In the left, which weighed 280 grm., an area of congestion and petechial hæmorrhages in the upper pole gave evidence of ascending pyelonephritis. The bladder wall was also inflamed. Infiltrations of chloromatous material were seen in relation to the lesser curvature of the stomach, and between the lobules of the pancreas.

Skull and brain.—Similar greyish-green deposits lay in the deeper layers of the scalp and in the dura mater covering the brain, and the folds of the falx cerebri and tentorium cerebelli were distended with similar greenish material. The lateral sinuses were filled with a pale clot. The infundibulum was also swollen and green and the basisphenoid in its upper part was replaced by chloromatous material which projected forward from it into the sphenoidal sinus as a cauliflower-like excrescence pushing the floor of the sella turcica upwards. Masses of greenish material were also found in the orbits lying on the orbital fat. These were more abundant in the left orbit than in the right.

The choroid plexus of the fourth ventricle was enlarged and bright green in colour.

Apart from the infiltration of the infundibulum, no green masses could be seen within the substance of the brain.

Spinal cord.—On removing the vertebral laminæ a deposit of grey green soft material was seen lying on the dura mater over the last cervical and the first seven thoracic segments and passing out a short distance through the intervertebral foramina. Similar deposits lay on the dura mater covering the anterior surface of the lumbar enlargement. On opening the dura mater the cord was seen to be slightly thinned and avascular at the level of the fourth, fifth and sixth thoracic segments.

Histologically the chloromatous masses and infiltrations all had an identical structure, being composed of masses of cells with rounded or lobed nuclei and a small amount of cytoplasm which stained fairly intensely with eosin. Some rather larger cells contained large, highly refractile granules which also tended to stain with eosin. A number of smaller cells indistinguishable from the eosinophil cells of the blood were also present. With benzidine staining, the cytoplasm of all the smaller cells showed oxydase granules and the granules of the larger cells also stained brown with this method. The latter granules also stained red with Scharlach R. in frozen sections and appeared to be a form of lipochrome. Apart from the numerous capillary vessels there was remarkably little stroma in the chloromatous masses, but fine reticular and collagenous threads could be seen passing through the tissue in all directions. (See fig. 1.)

The cord was examined at the level of every segment by a variety of staining methods. The most striking peculiarity was the presence in almost every vessel of a plug of leucocytes and myelocytes forming a fairly solid mass. Acute chromatolysis of some of the nerve-cells in the anterior horn was seen in the eighth cervical and first dorsal segments, and in the lumbar enlargement from the third lumbar to the first sacral segments. This appeared to be due to the passage of the emerging roots through the chloromatous masses in relation to the dura mater. At the level of the cord, which was observed to be thin and pale, viz., the fourth, fifth and sixth thoracic segments, a striking change was seen in the white matter, especially in the lateral columns. This consisted of areas of fenestration sometimes on the surface of the cord, but as often more deeply placed, and in some cases close to the grey matter. In these areas a large proportion of the nerve-fibres were swollen, their myelin sheaths either being broken up into fatty granules or stretched out into a thin peripheral ring. Within this ring two forms of body could be seen, one a nucleated cellular mass taking a faint blue stain in Scharlach R. sections and containing fine granules of degenerating myelin; the other a rounded homogeneous "cytoid" body, which on focusing proved to be a swollen axis cylinder. In longitudinal sections the fenestrated areas were seen to consist for the most part of rounded rather than elongated swellings of the myelin sheaths in which the myelin was broken down into granules, most of which did not stain very intensely with Scharlach R., but retained the double refractility of myelin and were, therefore, probably cholesterin compounds. In similar sections stained by Bielschowsky's method the axis cylinders, as they passed through these

swollen areas, were seen to be swollen to more than twice their normal width. In some cases this swelling was oval or almost globular, in others more fusiform. Although these rarefied areas were usually situated in relation to one or two small blood-vessels, they were never concentric with the vessel, nor indeed were they of any fixed pattern. Those near the surface were more or less wedge-shaped with their bases outwards and consisted of a diffuse vacuolation affecting only a small proportion of the fibres. The most intense area was present in one lateral column in the fifth thoracic segment (fig. 5). This was an oval zone with its long axis radially placed, lying midway between the grey matter of the horns and the surface of the cord. In it almost every nerve-fibre was affected and the large vacuoles were only separated from one another by a very thin layer of tissue. Very numerous swollen axis cylinders were seen in this area, not only in the vacuoles but also in the tissues in the vicinity where there was no vacuolation. In the eighth and ninth thoracic segments similar areas were present, but in these the degree of fenestration and of swelling of the axis cylinders was less intense. These areas seemed to extend only for a comparatively short distance in a longitudinal direction, as the nerve-fibres in the next segments above and below them presented no evidence of disease. (See figs. 2, 3 and 4.)

Apart from these fenestrated areas the cord was comparatively normal. Early tract degeneration, in the form of swelling and partial disintegration of some of the myelin sheaths, was seen in the tracts of Goll, Flechsig and Gowers in the cervical segments and in the pyramidal tracts in the lumbar segments. In these tracts no swollen axis cylinders were visible and the swelling of the myelin sheaths was only of minor degree.

Case 2.—F. M., male, aged 8, was admitted to Charing Cross Hospital under the care of Dr. Gordon Holmes, on March 3, 1928, with the history of frequent spasms of severe abdominal pain of a fortnight's duration. Examination revealed a complete left-sided facial paralysis; the abdomen was somewhat full in the right iliac fossa but in other respects was normal. Temperature 98° F., pulse 120, respirations 24.

The abdominal pain persisted despite treatment. On the tenth day after admission he was found to have retention of urine, the bladder being distended to a point a quarter of an inch above the umbilicus; a catheter was passed and 17½ oz. urine withdrawn. The following day the bladder was again distended and a penile erection was noticed. When the child was told to stand it was found that he could not walk. Examination of the legs revealed a flaccid paraparesis with absence of the knee-jerks. The ankle-jerks were obtained and plantar stimulation gave a flexor response. There was no defect of sensation.

Next day the boy could no longer feel pin-prick over the legs or trunk up to the level of the eighth rib anteriorly. Lumbar puncture yielded a distinctly yellow fluid, containing a fine fibrin web. Total protein measured 1·3 per cent. with a marked excess of globulin. Cells numbered 2 per c.mm.

Within the course of the next few days the level of anæsthesia mounted as high as the sixth rib. A second lumbar puncture yielded a yellow fluid which clotted spontaneously in the test-tube.

A fortnight after the onset of paraplegia, nodules were felt in the groins. The child gradually grew paler and more listless, and developed several trophic sores. The degree of paraplegia became absolute with a total areflexia below the level of the lesion. The left-sided facial palsy was now much less noticeable.

A blood-count at this period revealed: Reds 3,150,000, Hb. 44, C.I. 0·7. Whites 15,700, polymorphs 54·3 per cent., large hyaline 0·3 per cent., small lymphocytes 22·3 per cent., myelocytes 20 per cent., myeloblasts 3 per cent. Some degree of poikilocytosis and anisocytosis.

The nodules in the abdomen became gradually larger but the spleen was not palpable until six weeks after the onset of paraplegia. A week later three nodules were felt on the scalp. The child now became still drowsier and lost weight. Purpuric patches appeared in the skin. Pains were complained of in the head, chest and ears. The general condition deteriorated markedly and there were bouts of generalized tremor. The child died on May 22, 1928, eighty days after admission to hospital.

Throughout the course of the illness the temperature had been raised, at times reaching as high as 104° F.

Autopsy was performed the next day by Dr. Gordon Holmes.

Thorax.—Flat masses of deposit lay on the outer aspects of the ribs and posterior surface of the sternum. A large mass was present on the right side of the vertebral column projecting into the pleural cavity. Soft glands were seen at the roots of the lungs, and section of both organs showed infiltration. The heart was normal except for a gland on the anterior aspect of the pericardium.

Abdomen.—There was a chain of retroperitoneal glands in the abdomen.

Spleen.—Enlarged, weight 200 grm.

Liver.—Weight 810 grm.

Kidneys contained numerous small areas of growth, chiefly in the cortex. Two glands were found in association with the wall of the bladder.

Skull.—Several flat, soft, greenish nodules lay beneath the aponeurosis of the scalp. When the brain had been removed, other similar tumour masses were found. The meninges were infiltrated in various places, notably at the anterior end of the falx and in the dura covering the temporal bones, the basi-occipital and the lateral sinus. Masses of growth lay underneath both petrous bones.

Spinal canal.—Large greenish masses were seen in the epidural space ringing the cord at the level of the eighth cervical and the first thoracic segments. Flatter, more sessile masses were also found lying on the dura mater which covered the lower six thoracic segments. (See fig. 5.)

On cutting through the dura mater the cord was found to be pale, but otherwise normal down to the eighth thoracic segment, but from this level downwards it was shrunken and brownish, and adherent to the dura mater. From the ninth to the twelfth thoracic segments the central part of the cord was quite diffluent. In the lumbar segments it was less softened, although here also no trace of the normal structure of the cord could be seen.

As it was considered advisable to retain the cord as a museum specimen thin transverse slices were taken only from the first thoracic and the ninth thoracic segments. These were embedded in celloidin and stained by Nissl's method (toluidin blue), hæmatoxylin and van Gieson, Mallory's aniline blue—Orange G. and Loyez myelin sheath stain.

Sections from the first thoracic segment showed little abnormality except a fairly severe degree of chromatolysis in some motor cells of the antero-lateral and postero-lateral groups, and degeneration in the columns of Goll and Flechsig. In these tracts there was some degree of vacuolation of the cord caused, apparently, by swelling of the myelin sheaths and disintegration of the myelin similar to that seen in the cervical segments in Case 1. It seemed to correspond to an early stage of ascending tract degeneration.

At the level of the ninth thoracic segment there was complete disintegration of the nervous tissue of the cord. The meninges were considerably thickened. The outer layers of the arachnoid were infiltrated with polymorphonuclears and larger cells with lobed or rounded nuclei similar to those seen in the chloroma masses in Case 1. Similar cells were also seen in the septa of the anterior roots, in which also many of the nerve-fibres were considerably swollen.

In the cord it was only possible to distinguish any of the original structure by the greater vascularity and the larger number of nuclei in the region of the grey matter. The capillary vessels here seemed to be considerably more numerous than normal and were linked to one another by thin collagen strands. Otherwise the tissue consisted almost exclusively of masses of fat granule cells, among which were a few small rounded nuclei with an unrecognizable cell body. In one anterior horn were the degenerated remains of three or four nerve-cells. These consisted chiefly of lipochrome granules with the remains of the nucleus, as the cytoplasm had been almost entirely absorbed by mononuclear phagocytes. Fat granule cells were also found in large numbers infiltrating and distending the meshwork of the pia mater in the antero-mesial fissure and around the margin of the cord. (See figs. 6 and 7.)

Case 3.—J. W., male, aged 15, was admitted to Charing Cross Hospital on November 6, 1922, under the care of Dr. Gordon Holmes. Five days previously his legs had suddenly become weak and felt numb. There was at the same time some hesitancy in commencing micturition.

On examination he was found to be well nourished but pale. There was a flaccid paralysis of both legs with impairment of sensation up to the level of the second lumbar segment. The knee and ankle jerks were exaggerated; both plantar responses were extensor in type. There was an absence of sweating below the waist-line. There was no loss of sphincter control.

In the course of the following month the legs became still weaker; he developed incontinence of urine with retention. The right arm was also found to be weak and the biceps-jerk on that side was unobtainable. Small glands were felt in the axilla and the groin.

Two weeks later the weakness in the arm had disappeared. The legs

were now becoming spastic and involuntary flexor spasms occurred. The patient began to complain of pains radiating round the waist and down the right thigh. The lymphatic glands were now definitely enlarged and the spleen was palpable. A blood-count at this stage showed: reds 3,800,000, hb. 62, C.I. 0·8. Whites 16,000, polymorphs 20 per cent., lymphocytes 55 per cent., lymphocytes (large) 17 per cent. A few myeloblasts, myelocytes, and normoblasts were seen. There was polychromophilia and slight poikilocytosis.

Ten weeks after admission to hospital he developed a paralysis of the left side of the face and of the palate; he became deaf in the left ear. The paraplegia was now more profound and the upper level of analgesia had extended as high as the seventh thoracic segment.

Three months after admission nasal and conjunctival hæmorrhages appeared.

Three and a half months from the time of entry into hospital a condition of leukæmic retinitis first made its appearance; the discs were swollen, the veins engorged, hæmorrhages and white patches of exudate were visible in the retina.

Following treatment by X-rays some degree of improvement in the legs resulted and also in the sphincter control. The retinitis advanced, however, and the patient's general condition deteriorated. He developed deafness and a profound visual defect; purpuric areas appeared over the legs. Death occurred four months after admission.

At the autopsy typical leukæmic changes were demonstrated in the viscera. No morbid change was demonstrable in the brain. The spinal cord and its membranes, however, were the seat of various pathological processes:—

(1) A few small hæmorrhages were visible in the pia-arachnoid.

(2) Two large epidural leucoma-masses were present at the second and seventh thoracic levels respectively.

(3) The underlying cord showed only slight changes of compression, being somewhat œdematous and containing a few hæmorrhages.

(4) The spinal roots were in many places infiltrated by leucoma-masses.

Case 4.—J. P., male, aged 11, was admitted to the Queen's Hospital Birmingham, under the care of Dr. Mackey, on April 5, 1926. Symptoms began with a seven weeks' history of pain in the dorso-lumbar region, particularly on the left side. He became weak and lost flesh; three weeks before admission his legs became weak, preventing him from walking. At the same there was a little difficulty in commencing micturition. The legs grew weaker until a state of complete paraplegia supervened five weeks after the onset of symptoms.

Examination revealed a pale wasted boy with proptosis of the left eye. The right side of the face was swollen and the veins over the right side of the forehead were more dilated.

The abdomen was protuberant, and the superficial veins were dilated. The liver was enlarged to the extent of three fingers' breadth below the costal margin. A large mass was palpable in the lumbar region, irregular in outline, extending from the costal arch above down to the iliac crests. The spleen could not be felt.

The motor and sensory systems were normal over the arms and upper part

of the trunk. The lower extremities were completely flaccid and powerless. Postural and vibratory sense were lost in the legs but tactile and painful stimuli were correctly appreciated. Knee and ankle jerks were absent; there was a bilateral Babinski response.

Cerebrospinal fluid examination gave the following report: Straw-coloured fluid, no cells. Marked excess of albumin and of globulin. Sugar 19 mg., chlorides 0·8 grm. per cent.

Skiagraphy revealed: (1) a mediastinal tumour and (2) an erosion of the anterior surface of the second lumbar vertebræ.

The clinical diagnosis was made of a bilateral suprarenal tumour with metastases in the mediastinum and spinal canal.

Whilst in hospital the patient became more cachectic and drowsy: there were frequent slight epistaxes. Pains in the legs were constantly complained of, and vomiting was an occasional symptom. He finally became comatose and died two and a half months after the first symptom.

The autopsy was performed the following day by Dr. O. Brenner.

Spine and spinal canal.—In the dorso-lumbar regions there was a soft, red mass resembling partially organized blood-clot, wrapped closely around the spinal cord. The cord itself appeared normal except for a small red spot in the right anterior horn in the lumbar region. The consistency of the second lumbar vertebræ appeared softer than usual.

The changes in the visceral organs were characteristic of leukæmia. The thymus was greatly enlarged with areas of focal necrosis visible on cross-section. The spleen was shrunken and atrophic; weight, 50 grm.

Both kidneys were uniformly much enlarged (weight: right 540 grm., left 530 grm.).

Some of the lumbar and many of the mesenteric lymph glands were enlarged.

Longitudinal section of the femur showed that it was filled for about two-thirds of its length with a greyish-red gelatinous marrow.

Histological examination (Professor Haswell Wilson) of the spinal cord revealed a leukæmic infiltration of the meninges and of the sheaths and interstitial connective tissue of the anterior and posterior nerve-roots. The process spread into the cord via the anterior fissure and the sheaths of the blood-vessels. The nerve-cells, with one or two exceptions, were normal. Microscopic examination of the viscera showed a generalized leucocytic infiltration.

There are a number of cases on record similar in essentials to these four cases described. The majority had the characteristics of chloroma, although pure leukæmia has been diagnosed in some.

Eichhorst's case [7] illustrates such focal aggregation of leucocytic material outside the spinal cord. His patient, a young man of 17, was admitted to hospital for enlargement of the glands and general weakness. While an in-patient he developed in the course of a week a spastic paraplegia, with sensory loss and bladder trouble. The blood examination

gave the picture of a myeloid leukæmia. At autopsy it was found that the fifth, sixth and seventh segments of thoracic cord were compressed by a greyish tumour-mass of glandular appearance about 3 cm. long lying along the posterior aspect, especially on the left side. The cord at that point was severely compressed and softened, and secondary degeneration could be traced above and below the site of the mass.

Harris and Moore in 1902 [10] demonstrated before the Manchester Pathological Society the spinal cord of a case of chloroma occurring in a boy of 14. The first symptom was severe pain of sciatic distribution persisting up to the time of death. Two weeks before the end he became partially paralysed in arms and legs. At the post-mortem examination a nodular mass was found on the inner aspect of the dura and the periosteum of the vertebræ.

In the same year, Rosenblath [29] described a case of chloroma in a boy of 15, who complained of pain in the sciatic region when the leg was extended; although the knee-jerks became sluggish no actual paralysis supervened. The patient died, and the pathological aspect was studied by Rosenblath and also independently by Risel [27]. A mass of chloromatous material lay between the bone on the inner aspect of the lumbar spine and the dura mater; a similar mass measuring 10 cm. by 1 cm. was present in the lower thoracic region. The posterior roots in the lumbar segment as well as the sacral plexus were implicated in the masses. Histological examination of the cord revealed a degeneration in the posterior columns above the area of root damage.

A case of chloroma in a male of 19 was recorded in the following year by Gumbel [9]. This patient developed four weeks before death the signs "of a beginning myelitis." Pathological examination showed an infiltration of the epidural fat with green tumour-masses, involving especially the nerves of the lower sacral region. The anterior and posterior roots of the lumbar segments were thickened in sausage-like manner. The spinal cord was constricted at the cervico-dorsal junction, and in the dorso-lumbar region the cord was softened.

Weinberger (1907) [40] reported the case of a lad of 15 who complained of stiffness of the spine for one month before admission. Pains later appeared in the left thigh, and there was some difficulty in micturition. Whilst in hospital he developed weakness in the arms and legs, with dysæsthesiæ and defective sensibility. The tendon-jerks were increased, there was ankle clonus and bilateral Babinski responses. He became doubly incontinent. After death infiltrating thickenings of

chloromatous material were found in connection with the periosteum and dura of the posterior part of the spine, especially in the thoracic region. The cord itself was severely compressed.

In 1909 Saltykow [32] described a female patient of 37 who showed, two months before death, a tumour in the left side of the neck and a weakness of the left arm. She was regarded as a case of tuberculous spondylitis, but at the autopsy a mass of chloromatous matter 1 cm. thick was found lying between the bodies of the vertebræ and the spinal dura. It extended longitudinally from the fifth to the tenth thoracic segments. The cord was compressed and softened.

Stursberg's case (1914) [38] was that of a man of 30 suffering from myelogeneous leukæmia who experienced a sudden pain in the back and legs. The following day both legs were completely paralysed and pain persisted in the legs. A condition of flaccid paraplegia with analgesia remained up to the time of death twelve days later. Pathological examination demonstrated a myeloid mass in the spinal dura compressing the cord, particularly in the lower dorsal and lumbar regions.

Sauer [33], in the same year, reported a case of chloroma in a man of 36. His symptoms were those of severe pain in the right leg with some defect of power, especially in dorsiflexion of the foot. There was tenderness on deep palpation over the course of the right sciatic nerve, and Lasègue's sign was positive on that side. Pain and thermal sensibility was diminished over the distribution of the third, fourth and fifth lumbar and the sacral segments. At the post-mortem examination it was seen that the whole of the anterior aspect of the spinal dura was covered with a layer of chloroma-material which became thicker towards the lower end.

Miermet's patient [21]—recorded in 1914—was a boy of 15, whose illness started with a sudden giving way of the leg. During the next four months the same symptom recurred four times, and at the end of that time he was admitted to hospital because he could not walk nor void his urine. A lumbar puncture gave a yellow fluid containing an excess of cells and of protein. The diagnosis of spinal tumour was made and a laminectomy performed. At operation the cord was found to be surrounded by "granulation tissue," and the case was then regarded as one of tubercle. An emulsion of the granulomatous tissue was, however, not lethal when injected into a guinea-pig. Later, a swelling developed at the site of the scar, and was thought to be a cold abscess. Then numerous blue-black lumps appeared, and the diagnosis

was changed to that of myeloid sarcoma. The case ultimately proved to be one of chloroma, however, and lumps of greenish-grey tissue were found in the spinal meninges.

Bassoe reported in 1918 a case of spleno-medullary leukæmia in a woman aged 28. Three years after the onset of her anæmic symptoms she developed a sudden chill; the day after, the legs were numb and so weak that she could not stand. She was completely paraplegic in the course of one day and two days later she became febrile. Difficulty in urination appeared next, amounting later to a complete retention. She showed an absolute paraplegia with loss of sensation up to the fifth rib; the tendon-jerks were absent except the left ankle-jerk, and plantar stimulation gave extensor responses on both sides. There was pain on pressure over the fourth, fifth and sixth thoracic spines. The patient was persistently febrile and developed bedsores; she died five weeks after the onset of paraplegia. In addition to the typical visceral manifestations of leukæmia, there was found at autopsy a thickening of the dura in the fourth, fifth and sixth thoracic regions which was firmly adherent to the bodies of the vertebræ. The cord was surrounded by thickened and infiltrated membranes causing partial necrosis of the spinal parenchyma, especially in the posterior aspect in the fifth thoracic segment.

In the following year a further case of chloroma with deposits in the spinal meninges of the mid-thoracic region was reported by Lewis [18]; unfortunately there are no clinical details as to the neurological manifestations in the legs.

Heissen's valuable paper appeared in 1925, and in it he quoted a case of chloroma occurring in a woman of 34. For five weeks she complained of backache and for two weeks of cramps and stiffness in the legs. The day after the first appearance of this latter symptom, dysæsthesiæ were noted in the left leg At the same time she suddenly lost power and sensation in the lower extremities and became incontinent. On examination a state of flaccid paraplegia was encountered with sensory loss up to the nipples. The reflexes were unobtainable; bladder and rectum were paralysed. The cerebrospinal fluid was cloudy and escaped slowly from the needle; the pressure measured only 70. There were 375 cells per c.mm. including polymorphonuclears and immature myelocytes. The total protein was markedly increased. Death occurred seventeen days later. At autopsy a layer of green chloromatous deposit was found outside the dura of the second to fifth segments of the thoracic spine. The cord in this area was compressed and on trans-section showed softenings and hæmorrhages.

In the same year, Sturrock and Jeffery [37] demonstrated at the pathological meeting of the Neurological Section of the Royal Society of Medicine a specimen of chloroma in the vertebral canal causing paraplegia. The patient was a boy of 14, in whom paralytic signs had developed four weeks before death. Fuller clinical details are unfortunately not given.

(5) Symptoms of a paraplegic order may also occur in chloroma from *infiltration of the spinal roots of the lumbar and sacral plexuses* without any actual compression of the cord. An example of this type is illustrated by the case recorded by Klein and Steinhaus (1904), [17]; their patient, a man of 38, had complained for six weeks of pain in the right leg and examination yielded signs regarded as evidence of neuritis of the right sciatic nerve. Autopsy revealed numerous chloromatous nodules along the vertebral column, not compressing the cord, but surrounding the roots.

(6) Another rare cause of paralytic manifestations in association with the leukæmias is to be found in the occurrence of changes *in the peripheral nerves*. Instances of "leukæmic polyneuritis" were referred to by Müller in his Inaugural Address of 1895 [24]. A particularly striking example was published by Wilfred Harris (1921) [11] and [12]: A youth of 17, complained first of weakness of the legs: five weeks previously the legs had become stiff and a fortnight later he became unsteady on his feet and noticed numbness and tingling of the fingers. The gait was feeble and uncertain, there was weakness of dorsiflexion of the feet with partial reaction of degeneration in the leg muscles. Tactile and pain sensibility were diminished up to the knees. Patellar, Achilles and fore-arm jerks were absent and no plantar response was obtainable; the cremasteric reflexes were normal. There was no sphincter disturbance. The patient died about twelve weeks after the onset of symptoms. Post-mortem revealed the typical changes of leukæmia with leucocytic infiltration of the peripheral nerves. Harris did not regard the paretic manifestations as the result of the infiltration of the nerves, but rather as an expression of a polyneuritis due to an obscure toxin.

Infiltration of the peripheral nerves in leukæmia was also mentioned by Ball, in the discussion following Holmes's paper at the Association of Physicians.

(7) The last anatomo-pathological process which may be responsible for the presence of spinal symptoms in the leukæmias is seen in those very rare cases of *combined degeneration of the cord*. Although the

great majority of instances of funicular myelitis or subacute combined degeneration of the cord are clinically associated with a morbid blood-picture which approximates to the "pernicious" anæmia type, nevertheless departures from this type are common. Thus, one may meet with cases of severe spinal signs accompanied by a normal blood-count. Moreover, the characteristic clinical or pathological manifestations may—very infrequently—be associated with other hæmatological disorders, such as Hodgkin's disease (McAlpine [20]), streptococcal anæmia (Lorimer [19]), chronic icterus (Minnich [22]), and Addison's disease (V. Kahlden [16]), as well as sprue and malaria. According to Collier [5] they may also occur in the leukæmias, but detailed clinical and pathological reports of typical cases of this association are wanting although there are some suggestive records in the literature [32].

In the original monograph of Minnich (1892) on spinal disease in pernicious anæmia, there are a few brief references to the occurrence of similar pathological changes in a case of leukæmia, and Minnich reproduces illustrations of the spinal cord which show degeneration in the posterior columns. We are told that this case was without neurological signs or symptoms during life.

Two years later appeared Müller's thesis in which he described the spinal cord changes in a case of splenic leukæmia. Unfortunately no clinical data are available. He found a slight sclerosis in the columns of Goll and partly also in those of Burdach, with loss of nerve-fibres and increase of neuroglia. This process was most intense in the cervical region. The ground bundles contained some degenerated fibres and lacunæ. There were no changes in the grey matter or in the anterior or lateral zones of the white substance. The blood-vessels and the anterior and posterior roots were normal.

Nonne [25] in 1897 reported clinical and anatomical details of two fatal cases of leukæmia, in neither of which had there been any neurological signs during life. In the first case (that of a man aged 59) there were numerous small foci of change in the myelin, especially in the cervical cord. The axis-cylinders were swollen in these areas and in the intervening substance the neuroglia had proliferated. These foci were so minute as to elude perfunctory search; they were asymmetrical in distribution and lay chiefly in the anterior pyramidal tracts, the lateral columns and the posterior columns, in this order. There was no anatomical association between the foci and the blood-vessels. In addition to these changes, there was a slight sclerosis of Goll's columns in the cervical region, and also to a less extent in the upper and mid-

thoracic portions. Nonne's second case (a man aged 31) was also characterized pathologically by focal changes in the white matter, especially in the anterior columns. No sclerosis of Goll's or Burdach's columns was seen in this case.

Gordinier and Lartigau in 1902-3 [8] described a case of lymphatic leukæmia in which a sclerosis of the posterior columns was demonstrable in the upper thoracic region of the cord after death. We have been unable to secure clinical and histological details of this case.

The only instance of this kind associated with chloroma is of doubtful authenticity. Dock and Warthin in 1904 [6] reported a fatal case of chloroma in a man aged 45. No objective or subjective signs were present referable to the central nervous system. At the autopsy the spinal cord appeared normal, but histological evidence of "atrophy and degeneration" was present.

Pathological Discussion.

Throughout this paper no separation has been made between neurological syndromes complicating the leukæmias and those occurring in association with chloroma. This arrangement has been followed in accordance with the modern conception of leukæmia and chloroma as being of essentially similar nature. The latter clinical state is differentiated primarily by a greater tendency towards the formation of "heterotopies," or leucocytic infiltration *en masse*: secondly, by the presence of a characteristic green tint to the cell-masses; and thirdly, by an acute course. Heterotopies may, however, occur in other varieties of leukæmia, as evidenced by the so-called "leucosarcomatosis" of Stursberg, and the cases spoken of as chlorosarcoma. Typical green coloration may also be seen in the other types of leukæmia. We are justified, therefore, in treating chloroma and all other forms of leukæmia as varieties of a wider group of hæmoblastosis, in the sense of Orth.

Although the number of instances of spinal involvement in the course of leukæmia is not sufficiently great to warrant dogmatic conclusions, it appears that certain varieties of pathological change are more prone to occur in particular hæmatological types.

In some cases there may be a diffuse permeation of the grey and white matter of the cord with cell-elements which do not form dense heterotopies. A reactionary gliosis may follow so as to produce a diffuse sclerosis of the cord. This variety of pathological change seems confined to the leucoses proper. At times the cell-elements may become aggregated here and there to form focal leucoma nodules which—unlike the heterotopies—are situated strictly within the spinal medulla.

The commonest cause of spinal symptoms in the leukæmias is obviously an infiltration of the spinal meninges with leucocytic masses. This process is more frequent in association with the clinical picture of chloroma. Thus out of a total of seventeen cases twelve were developed in connection with chloroma and five with leukæmia. The neoplastic cell-masses usually lie between the inner aspect of the vertebræ and the spinal cord. They are more or less firmly adherent, either to the periosteum of the vertebræ or to the dura mater. In any case the epidural fat becomes infiltrated and ultimately replaced by the heterotopy. The infiltrating mass may lie anteriorly or posteriorly, or may totally encircle the cord. As a rule the mass is of some length and may extend from one end of the cord to the other. The infiltrations are smooth in appearance and vary in tint from white or pale yellow to a distinct green; they are india-rubber like in consistency; German writers often describe them as resembling the rind of bacon (Schwarte). It may be possible by exercising care to dissect the masses off the periosteum or dura mater.

Frequently the infiltration spreads so as to involve the anterior and posterior nerve-roots; rarely, the roots alone are implicated. Sometimes the infiltrating tissue follows the course of the roots and insinuates itself into the paraspinal fascia and muscles via the intervertebral foramina. At times the opposite process is demonstrable; that is, the heterotopy may take origin in the tissues lying alongside the bony column, and following the posterior primary divisions of the dorsal nerves, enter the spinal canal by way of the intervertebral foramina.

The secondary changes in the spinal cord vary from one case to another. In some cases at the level of the largest cellular masses the cord appears constricted and pale, and cross-section shows an anæmic cord in which the grey matter can scarcely be distinguished from the white columns. The pia mater over this region shares in the ischæmic process by loss of the fine vascular ramifications. In other cases the cord is obviously hyperæmic at the site of the tumour; it is swollen and injected and on cross-section pin-point hæmorrhages may be seen in it. This appearance, which is reminiscent of that of acute myelitis, is distinguished from it by the absence of cellular exudate, and is probably the result of acute infarction. In fact it appears probable that both the anæmic and the congested appearances may be caused rather by the obstruction of blood-vessels than by the actual compression of the spinal cord by the cellular masses.

Compression of the cord may undoubtedly also play a large part in

the pathogenesis of the condition, as is shown by the slowly progressive history in some cases, but in others the fulminating onset of the paraplegia is more suggestive of a thrombotic softening of the cord.

The condition of the spinal cord in our second case indicates how severe and extensive this condition of ischæmia may be. In it the lower part of the cord from the ninth thoracic segment downwards was completely disorganized with the disappearance of all the nervous structures, and persistence only of the walls of the blood-vessels, the membranes and the connective tissue septa. Such a condition must be caused by a widespread deprivation of blood supply, and can be paralleled in our experience only by cases in which many of the intervertebral arteries have been obstructed or compressed by tumours or bony overgrowth. In the cases under discussion it is easy to see how such a vascular obstruction might occur. It has been noted that the cellular masses frequently pass out through the intervertebral foramina compressing the nerve-roots, and in doing so are likely to compress also the segmental arteries and veins. Thrombosis of vessels may also be caused by the degenerative changes in the walls of the vessel or by the leucocytic clots inside them which have been seen in some cases. But these appearances may be secondary to the ischæmia rather than the direct cause of thrombosis. In any case it seems probable that the severer degrees of myelomalacia which have been described in association with the meningeal infiltrations of chloroma and leukæmia should be attributed rather to ischæmia than to direct pressure.

It is, however, more difficult to decide the pathogenesis of the small areas of softening or fenestration which Nonne described in his two cases and which were present in our first case. That the condition was the same in Nonne's cases and our own is clearly demonstrated by the beautiful drawings illustrating Nonne's paper which might equally have been drawn from sections of our case.

This pathological condition resembles in many details that seen in subacute combined degeneration of the cord, but differs from it not only in its patchy distribution, but also in the great swelling of the axis-cylinders associated with it. Nonne accepts the swelling of axis-cylinders as being an early stage in the process of fenestration, and this view is supported in our opinion by the presence of swollen axons round the periphery of the fenestrated areas. It is possible that Schultze's case (1884) [34] represents a similar early stage spread over a wide area. No clinical details of this case are available beyond the bare statement that the patient was suffering from leukæmia. On examina-

tion of the spinal cord he found a diffuse swelling of the axis-cylinders throughout the spinal cord. This was most evident in the cervical enlargement and in the lateral (and to a minor degree the posterior) columns. There was no trace of inflammatory cells. Schultze regarded the pathological condition as a disorder of the nutrition of the axis-cylinders as a result of the abnormal blood condition and compares it with a similar swelling of the axons of the spinal cord which he had found in cases of nephritis.

Similar swelling of axons has been described by Gordon Holmes [15], and by Roussy and Lhermitte [31] in concussion of the spinal cord by wounds. The latter authors call the condition "acute primary degeneration of myelinated fibres," and point out that the swellings on the axis-cylinders are always terminal and indicate fragmentation or rupture of the axons. That this condition may be due to a variety of causes which diminish the vitality of the neurons in the cord is indicated by its occurrence in such diverse conditions as injury of the cord and leukæmia. In the latter case it probably indicates a local necrosis of the more specialized nervous elements resulting from ischæmia of rapid onset. This theory of origin does not at first sight agree with Nonne's observation that the areas of fenestration do not appear to have any relation to blood-vessels. In our case a few small vessels were usually seen either in or close to them, but since the spinal vessels are more or less radially arranged it would be necessary to examine several transverse sections in order to prove this point with certainty. The fact that several of the most severely fenestrated areas were found somewhat deeply placed in the white matter, both in Nonne's cases and our own, may be taken as evidence against the view that they were caused directly by the pressure of a tumour or cell-mass, and indeed they are rarely seen in cases of spinal tumour. It seems, therefore, most probable that they form merely a variant or an early and partial form of the larger areas of myelomalacia which have been so commonly found in leukæmic cases. If this view be taken, it becomes impossible to ally the condition to the somewhat similar appearances seen in subacute combined degeneration. This is in accordance with the views of Weil and Davison [39], who in a wide survey of the literature could find no evidence that this form of spinal disease may be associated with leukæmia. It is true that in eighteen of their twenty-two cases of leukæmia and chloroma they accepted the clinical absence of paraplegic symptoms as evidence that no spinal disease existed, and did not confirm this pathologically. But if the fenestrated areas found by Nonne and ourselves were indeed an

early state of subacute combined degeneration of the cord, we should have expected that more typical and complete cases of the latter disease would have been found in association with leukæmia. That no such case has hitherto been published may, therefore, be taken as evidence against the relationship of the two pathological conditions.

It appears, therefore, that the most common factor in the production of paraplegia in cases of leukæmia or chloroma is anæmia or ischæmia of the spinal cord. The partial anoxæmia of the tissues which is inseparable from a severe anæmia must in many cases contribute to the effect produced by compression or thrombosis of the spinal arteries, but it is unlikely that any degree of anæmia which is compatible with life can, of itself, so lower the nutrition of the nervous tissue as to lead to its disintegration.

Clinical Discussion.

In the diagnosis of leukæmic paraplegia it is necessary to obtain accurate neurological observations on the degree of weakness, the extent of sensory loss, the state of the reflexes and the integrity of the sphincters. The importance of these points lies in the fact that in states of severe constitutional disorder such as occur in the hæmatopoietic diseases, a condition of "pseudo-paralysis" is apt to appear. This holds true, especially in the case of children, in whom weakness of the trunk and limb musculature or tenderness of the tissues may produce an akinesia algera which may closely simulate a paraplegia of spinal or peripheral origin. A highly instructive example in point is illustrated in the case recorded by Rolleston and Frankau [28]. Their patient, a boy of 5, had complained for five days of pain in the abdomen and difficulty in walking. When examined he was found to be unable to sit up, and there was tenderness over the lower dorsal and upper lumbar vertebræ. The paraspinal muscles were distinctly rigid. The case strongly suggested one of caries of the spine, but the subsequent appearance of enlargement of the liver, and of nasal, renal and retinal hæmorrhages, pointed to a leukæmia. A blood-count confirmed this diagnosis. At the autopsy typical leukæmia changes were found; the vertebræ were softened, but no actual lesion lay in the cord or its membranes and no spinal compression had occurred. In this case, therefore, the changes in the vertebræ set up pain and stiffness in the surrounding muscles, which accounted for the difficulty in sitting up and the pseudo-paraplegic symptoms.

When dealing with the symptomatology of the true paraplegic

manifestations of the leukæmias it will be well to consider first those cases with the pathological picture of masses infiltrating the epidural tissues as representing the commonest variety. Of the seventeen cases, including the four personal examples, fourteen were in males and three in females. The age at which symptoms appeared varied from 8 to 38 years, with an average of 20·6 years.

The early symptoms in the majority of cases were some subjective sensory complaint, usually pain. This is usually severe and is frequently of sudden onset. It is commonly referred to the back, but it may also affect one or both legs. In several instances this has led to the diagnosis of sciatica. Occasionally (as in Cases 1 and 2) the pain may be referred to the abdomen, suggesting—as in the former instance—the diagnosis of typhoid. Pain is not only the first symptom to appear in the majority of cases, but it is usually the most persistent feature. Sometimes the earliest symptom is a feeling of stiffness of the legs or of the muscles of the back. A sensation of numbness, deadness, or pins and needles is scarcely ever the initial symptom.

A short time after the onset of pain other clinical features appear. This interval is variable; in some cases it may be as short as a day, rarely is it longer than six weeks. At the end of this time the patient experiences, usually with some abruptness, dysæsthesiæ in the legs, accompanied or followed very shortly by weakness in the lower extremities. This latter symptom may be fulminating in appearance, being sudden in onset and immediately attaining its maximum intensity. At other times the paraplegia develops more gradually, so that a week or more elapses before the paralysis is complete. Once fully developed no improvement is to be anticipated as a rule, although in Case 2 some relief followed X-ray therapy. Objective sensory changes accompany the paraplegia and may be absolute in degree. Usually the subjective sensory disorders antedate by a short interval the appearance of objective change.

Bladder disturbances accompany the paraplegia and lead in the more severe cases to retention of urine and fæces. Sometimes, as in Case 2, difficulty in micturition may precede manifestations of paraplegia. Priapism is a characteristic, though rare, manifestation in leukæmia, and in the spinal cases may be the expression either of the paraplegia or of an actual leucocytic infiltration of the corpus cavernosum.

Bed-sores develop with marked rapidity once the paraplegia is established. In those instances in which laminectomy has been performed the operation scar may break down. Constitutional

symptoms appear either before or after the onset of paraplegia. The patient rapidly loses weight and becomes febrile. Visceral manifestations of leukæmia may develop at this stage and betray the true nature of the case, but it is important to note that frequently there are no somatic indications of chloroma or leukæmia until long after the development of spinal symptoms.

The physical signs in the cases of leukæmic paraplegia present nothing characteristic. It is perhaps striking how profound the degree of paraplegia may be; often the lower extremities are completely powerless and atonic, with tendon-jerks and plantar responses unobtainable. Percussion of the spine not infrequently reveals tenderness over certain of the spinous processes and rigidity of the para-spinal muscles is common.

A step-like ascent of the level of the paraplegia has been noted in certain cases. The level of the spinal lesion may at first lie in the mid-dorsal region, but, after an interval, signs may appear in the arms. Such a progression suggests either an upward spread of the epidural masses, or, alternatively, the development of focal softenings at a higher level of the cord.

Examination of the cerebrospinal fluid has been carried out in but few cases. In cases with complete spinal block the typical "loculation syndrome" is, of course, to be expected. The important diagnostic point in these cases, however, lies in the possibility of demonstrating in the fluid immature white cells such as myelocytes or myeloblasts (cf. Heissen's case). The presence of such cells would, of course, be diagnostic of myelogenous leukæmic paraplegia, but their absence in no way precludes the diagnosis.

In reviewing the case-reports contained in the literature, it is striking how often the true nature of the disease has escaped recognition until demonstrated at autopsy. The obvious reasons for this lie firstly in the intrinsic rarity of the leukæmic types of paraplegia, but the second and more particular cause depends upon the fact that the manifestations of disease of the hæmatopoietic system may be so slight as to be overlooked. It appears, therefore, that the occurrence of a sudden paraplegia, preceded for a time by severe pain in back or legs, and followed by fever, pallor and loss of weight should, when occurring in a young adult, suggest the possibility of a leukæmic or chloromatous origin. When such a neurological picture presents itself, it will be necessary by examination of the blood and blood-forming organs, to exclude this diagnosis.

The presence of local muscle atrophy in the legs with reaction of degeneration suggests an implication either of the spinal roots or of the

peripheral nerves. This process may occur as an isolated neurological state, in which case there will be an absence of the tendon responses and a peripherally distributed type of sensory impairment. On the other hand, the signs of lower motor neuron disease may be masked by coexistent paraplegic manifestations.

A point of great interest lies in the problem whether subacute combined degeneration of the cord may occur in cases of leukæmia. In most of the recorded cases in which a pathological appearance somewhat similar to that of this disease has been found in the cord, there were apparently no clinical manifestations to suggest any disease of the nervous system. It must be remembered, however, that in these cases the nature of the hæmatological disorder was recognized and, presumably, occupied the foreground of the clinical picture. Consequently, in the absence of gross paralytic signs, it is possible that certain minor neurological abnormalities, as slight degrees of cutaneous, postural or vibratory sensibility, may have escaped detection, and the severity of the general condition may have masked a weakness or ataxy of the legs with alterations in the reflexes. The routine investigation of the central nervous system in all cases of leukæmia may in the future settle this vexed question.

It is a pleasure to acknowledge the kindness of Dr. Gordon Holmes and Dr. Mackey in permitting us to quote the cases which were under their care.

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PLATE IV.

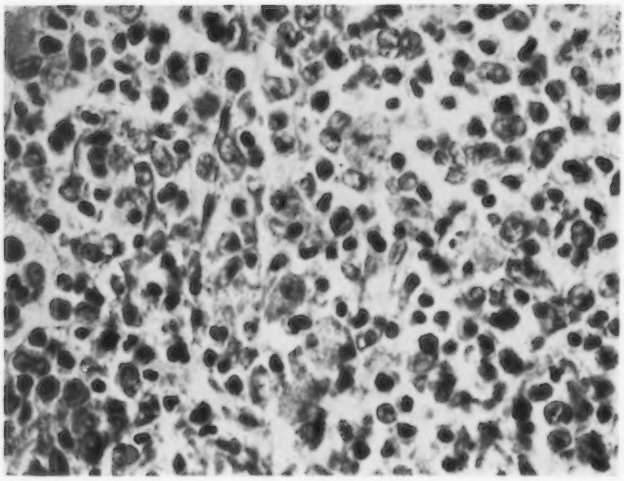


FIG. 1.

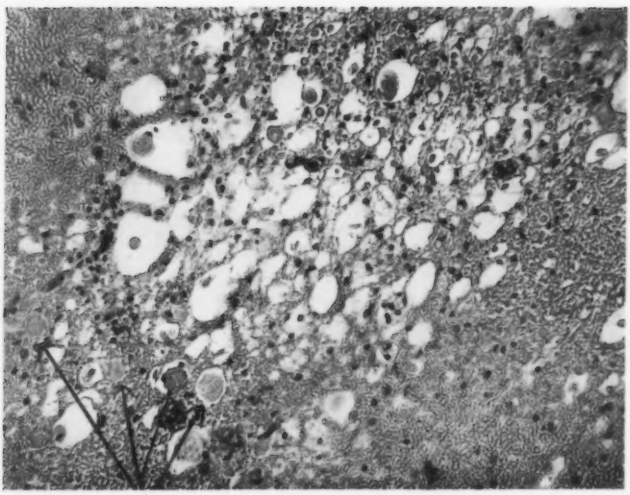


FIG. 2.

To illustrate paper by Macdonald Critchley and J. Godwin Greenfield.

PLATE V.

FIG. 3.

FIG. 4.

FIG. 5.

To illustrate paper by Macdonald Critchley and J. Godwin Greenfield.

PLATE VI.

FIG. 6.

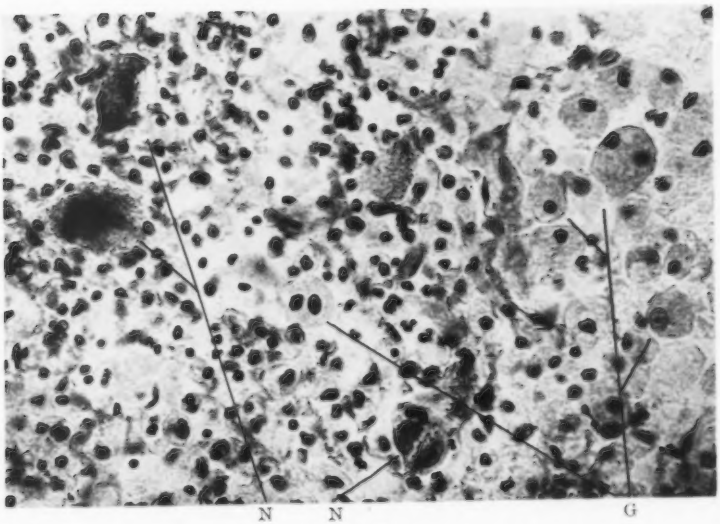
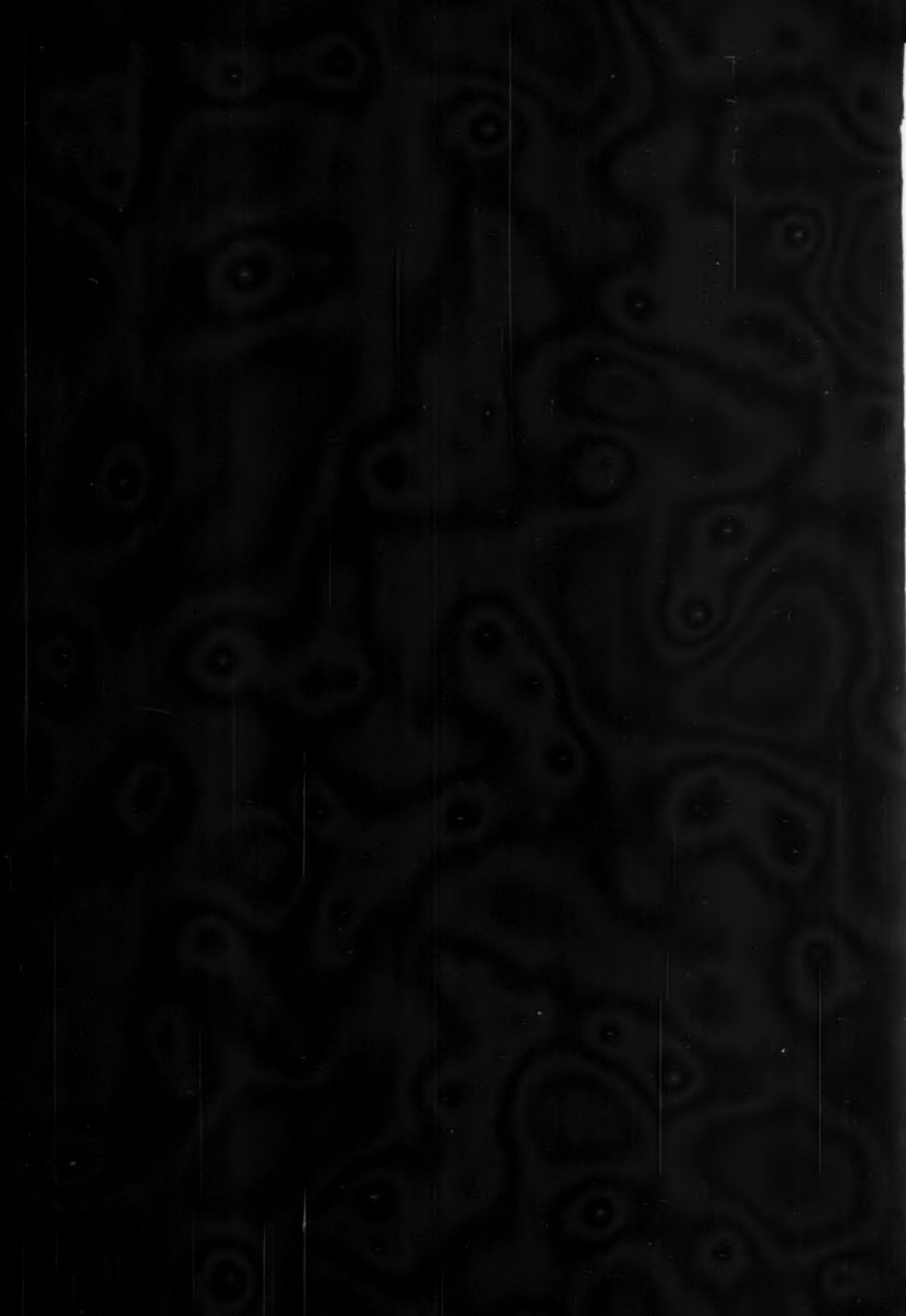


FIG. 7.

To illustrate paper by Macdonald Critchley and J. Godwin Greenfield.



DESCRIPTION OF PLATES.

FIG. 1.—*Case* 1. Cellular infiltration in falx cerebri. Three types of cell are seen: (1) Small cells with a darkly staining nucleus; (2) cells with a larger vesicular nucleus; (3) cells with a large cell-body containing lipochrome granules.

FIG. 2.—*Case* 1. Area of rarefaction in lateral column of fifth thoracic segment. Note the swollen axis-cylinders both in the vacuoles and in the surrounding tissues (A).

FIGS. 3 and 4.—*Case* 1. Transverse sections of the cord at the levels of the fifth and ninth thoracic segments (Loyez myelin stain). Areas of rarefaction are seen at both levels in the antero-lateral tracts.

FIG. 5.—*Case* 2. Drawing of spinal cord to show the cellular masses enveloping the dura mater.

FIG. 6.—*Case* 2. Low-power view of lower thoracic cord in transverse section. There is great thickening of the pia mater, except over the dorsal surface where it is broken through. The arachnoid is thickened in this position but not elsewhere.

FIG. 7.—*Case* 2. High-power view of the same section in the region of the ventral horn. The remains of three large nerve-cells are seen as nucleated granular masses (N). Elsewhere only fat-granule cells are present (G).

A CASE OF ARTERIOVENOUS ANEURYSM WITHIN THE BRAIN.

BY A. GURNEY YATES, M.D.,

AND

C. G. PAINE, M.B.

(*From the Pathological Department, University of Sheffield.*)

THE following case belongs to a group of intracranial vascular abnormalities to which Dandy has called attention in two recent articles [1], [2]. It presented somewhat striking clinical features, and the pathological changes subsequently found suggest a developmental origin.

W. Y., male, aged 32, was admitted to Fir Vale Hospital, Sheffield, on September 23, 1929. He complained of headache, defective vision and weakness on the right side.

History.—After a period of active service in France he returned to England in 1918, when he began to notice some weakness in the right arm and leg and slight intermittent headache. The onset was gradual. The symptoms at first were very slight. They slowly became worse, but he continued to do light labouring work until 1924, when he became unemployed. By this time the headache was almost continuous, with periodic severe exacerbations. It was worse in the early morning, and during severe attacks he had difficulty in speaking. At times he could not express what he wanted to say, and sometimes he found himself using the wrong word. His memory was poor, and his temper uncertain; at times he was quarrelsome and violent.

During the few months before admission to hospital, the pain in the head became more severe; it was localized in the left frontal region, behind and above the left eye, and it radiated down the left side of the face. Vision began to fail, the gait became much worse and there was a tendency to fall to the left. There were no fits of any kind and no vomiting, but frequent attacks of giddiness were complained of.

On admission to hospital the patient was mentally dull and at times slightly aphasic. The outstanding symptom was pain in the head. The sense of smell was normal on both sides. There was slight proptosis of the left eye. The pupils reacted normally, but the right was larger than the left. There was no nystagmus. Examination of the visual fields showed a right homonymous hemianopia. There was no optic neuritis, and the right disc was normal. The left disc showed no swelling and its outlines were clear, but the veins were enormously distended, and at the periphery, in the upper nasal quadrant, there

was a small aneurysmal dilatation. On one of the arteries near the disc were three tiny bead-like dilatations separated by constrictions. (Fig. 1.) The appearance of the veins when first seen was more striking than is actually shown in the picture, perhaps because the patient was lying down, whereas when the artist drew the fundus he was sitting upright in a chair. The ocular movements were normal in all directions. The fifth nerve was normal except for the pain which spread downwards over the left cheek. There was slight weakness of the lower part of the left face. The other cranial nerves were unaffected. The right arm was paralysed and spastic in flexion. All the deep reflexes were increased. There was no sensory loss. The right leg was spastic and its movements im-

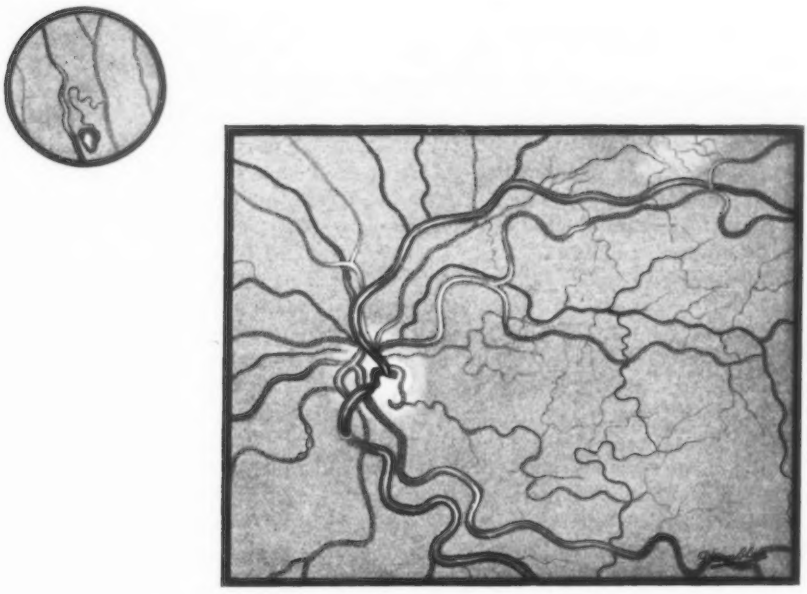


FIG. 1.

paired. All deep reflexes were increased and the plantar reflex was extensor. There was a partial loss of sensation in the foot. The left face, arm and leg were normal.

The only other physical sign was a blowing systolic murmur heard over the greater part of the head. It was loudest on the left side of the forehead, but it could be traced over to the right side, over both malar bones, and over the vertex nearly to the occipital region. There was no cardiac hypertrophy: the systolic blood-pressure was 110, and the diastolic 85. All other organs were normal.

The condition was thought to be an intracranial vascular lesion of the left

cerebral hemisphere involving both the motor and visual paths, and in view of the severity of the symptoms, and particularly of the pain which was increasing, an operation was decided upon. Mr. Brockman exposed the brain in the left fronto-parietal region in the hope of finding an afferent vessel passing to the lesion. Several enormously dilated veins were seen running over the surface of the brain. They were dark in colour and did not pulsate. Unfortunately the patient died before the operation had proceeded very far.

Post-mortem examination.—There was a hæmorrhagic effusion beneath the site of the dural incision. On removal the brain weighed 46 oz. There was a very definite pressure cone in the region of the medulla and inferior part of the cerebellum, and this was evidently the immediate cause of death. The left side of the brain was smaller and the convolutions appeared somewhat atrophic when compared with the right side, especially in the region of the left occipital lobe.

The most remarkable feature externally was a series of abnormal venous channels engorged with blood. One venous channel passed from the left lateral sinus across the dural space to reach the left occipital pole, where it ramified over the occipital lobe, smaller venous channels occupying the sulci of the cortex in this region. Some of the branches penetrated the substance of the occipital lobe where their course was subsequently traced.

From the left Sylvian fissure ran a large, distended, thin-walled blood-vessel, corresponding to the superficial Sylvian vein. This passed downwards, backwards and inwards to empty into a large venous space immediately above, and communicating with, the cavernous sinus, which was grossly distended. A large torturous and distended venous channel ran from here backwards, close to the under surface of the brain, and passed lateral to the fifth nerve between the point of its emergence from the brain-stem and the Gasserian ganglion. At a point where it crossed superior to the posterior cerebral artery it was joined by another large venous channel which communicated anteriorly with the distended left superficial Sylvian vein, which passed over the antero-inferior surface of the left temporo-sphenoidal lobe.

After receiving this tributary the vessel continued its course backwards lateral to the general line of emergence of the cranial nerve-roots, skirting the side of the mid-brain, until it reached the region of the posterior portion of the splenium of the corpus callosum. A large communicating vessel branched from it here and ran inwards to join the vein of Galen, which was also greatly enlarged. Subsequently, the vessel passed backwards and entered the substance of the brain through the left calcarine fissure, where it broke up into a number of smaller vessels, finally opening into numerous venous spaces within the substance of the occipital lobe and giving this part of the brain an appearance somewhat resembling that of a cavernous hæmangioma. The penetrating branches of the venous channel from the left lateral sinus to the occipital pole also divided up within the substance of the brain and joined this "hæmangiomatous" area within the occipital lobe. Thus a direct venous communication extended from the cavernous sinus anteriorly to the left lateral

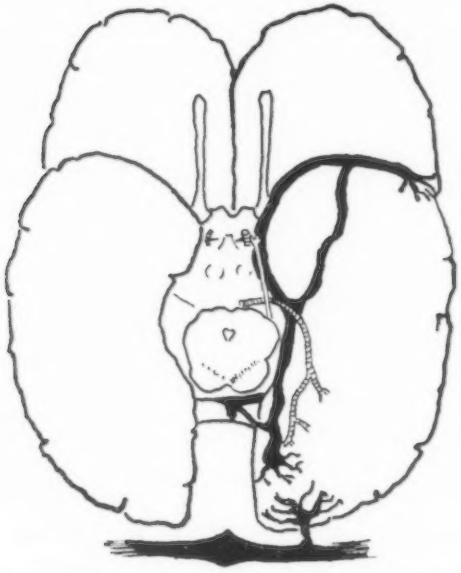


FIG. 2.—Diagram of base of brain showing the abnormal vascular channels.

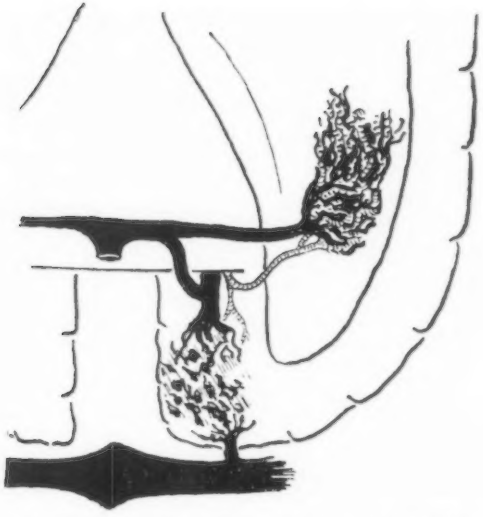


FIG. 3.—Diagram of section through left lateral ventricle and left occipital lobe, showing vascular abnormalities in the choroid plexus and occipital region.

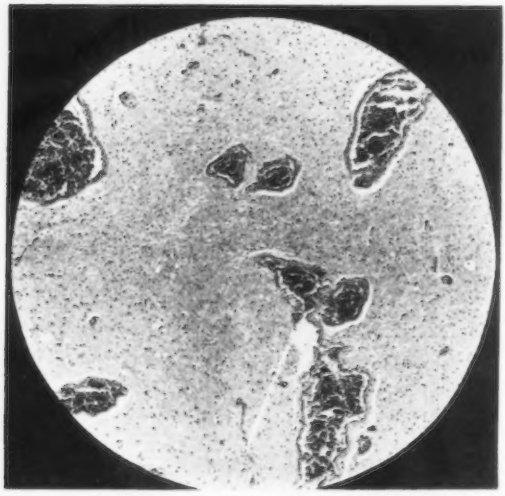


FIG. 4.—Photomicrograph of the occipital cortex, showing large numbers of thin-walled venous channels.

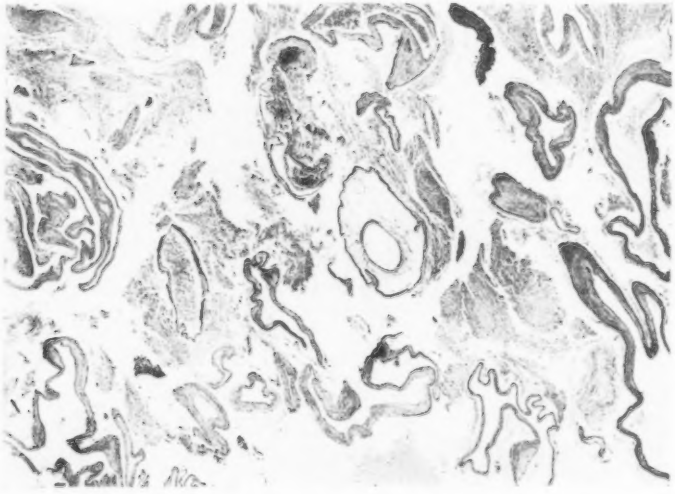


FIG. 5.—Photomicrograph of section through the choroid plexus.

sinus posteriorly, the direct communication being established by means of the large number of venous spaces within the substance of the occipital lobe.

A diagrammatic representation of the condition described is shown in figs. 2 and 3.

A photomicrograph of the occipital cortex is shown in fig. 4.

The arterial system also showed slight changes. The arrangement of the circle of Willis was normal. The basilar artery at its point of bifurcation divided into left and right posterior cerebral arteries, but the cross-sectional area of the left posterior cerebral artery was about three times that of the right. The posterior choroidal branches and the calcarine branch of this artery were correspondingly enlarged. A similar relationship was shown between the left and right veins of Galen, and whereas on the right side the choroid plexus of the lateral ventrical appeared normal, that on the left side was replaced by a twisted, worm-like mass of dilated vessels.

This condition is shown in diagram in fig. 3.

Fig. 5 is a photomicrograph of a section through the vascular mass which replaced the left choroid plexus.

The lateral ventricle on the left side was dilated and there was some general thinning of the surrounding cerebral cortex. The right ventrical appeared normal. In view of the fact that no obstruction to the free communication between the two ventricles could be found this dilatation of the lateral ventricle remains unexplained.

In order to exclude any direct arterio-venous communications that might have been overlooked in the dissection, the arterial and venous systems were injected in turn with an opaque paste and X-ray photographs taken. No such communication was found.

Discussion and Embryological Considerations.

Dandy, who has described a small series of similar cases, suggested that the condition is probably a congenital abnormality. An attempt has been made, therefore, to correlate the findings in this case with the development of the venous system of the brain and a possible explanation of the abnormal conditions is advanced.

Before dealing with the abnormalities of venous development in this case, brief reference must be made to the stages of normal development of the cerebral venous system.

At the base of the primitive brain-stem there exists a single channel, a continuation forwards of the anterior cardinal vein. The posterior end of this forms the jugular bulb and part of the lateral sinus, and the anterior end dilates to form the primitive cavernous sinus. Into this primitive cavernous sinus blood drains from the anterior part of the developing brain, more especially from a plexus of veins representing the superficial Sylvian group of veins. (Fig. 6, *a*.)

This primitive channel is reduplicated by another vessel passing forwards lateral to the otic vesicle, which joins behind and in front with the anterior cardinal vein. This channel is the vena capitis lateralis. With the growth of this secondary channel there is a subsequent atrophy of that part of the anterior cardinal vein between the jugular bulb and the cavernous sinus. (See fig. 6, *b*.) From the primitive cavernous sinus there grows forwards, upwards and then backwards, with the development and growth of the neopallium, a prolongation which subsequently

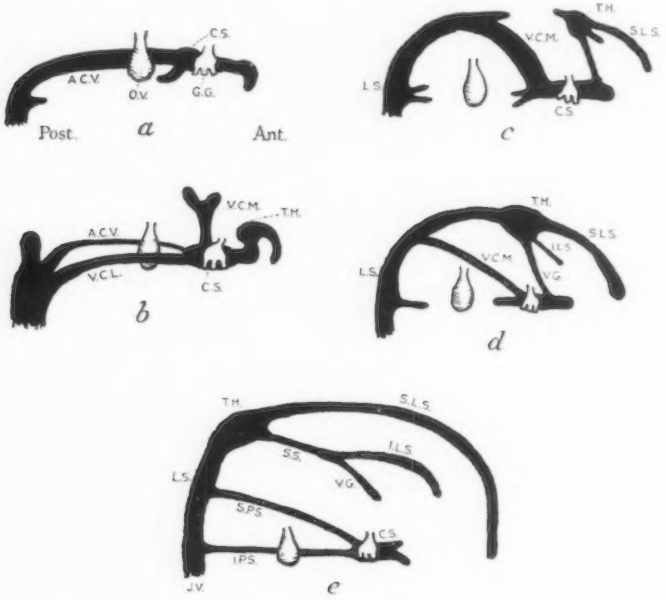


FIG. 6.—Developing venous system (modified from Quain's Anatomy). A.C.V., anterior cardinal vein. C.S., cavernous sinus. G.G., Gasserian ganglion. I.L.S., inferior longitudinal sinus. I.P.S., inferior petrosal sinus. J.V., jugular vein. L.S., lateral sinus. O.V., otic vesicle. S.L.S., superior longitudinal sinus. S.P.S., superior petrosal sinus, S.S., straight sinus. T.H., torcula Herophili. V.C.L., vena capitis lateralis. V.C.M. vena capitis medialis. V.G., vein of Galen.

forms the superior longitudinal sinus and the torcula Herophili. The residual venous channel between the primitive torcula Herophili and the cavernous sinus represents the vein of Galen. (Fig. 6, *c*.)

Normally, with the development of secondary venous communications by which drainage may take place, i.e., the formation of a junction between the torcula Herophili and the jugular bulb, and the upward growth of the vena capitis medialis which will later represent the superior

pretosal sinus, the primary blood-channels, more especially that part of the anterior cardinal vein between the jugular bulb and cavernous sinus, and also the vena capitis lateralis, atrophy and disappear. The primitive vein of Galen, being able to drain into the lateral sinus via the torcula Herophili, also loses its connection with the anterior cardinal vein. The stages of this evolution are shown diagrammatically in figs. 6, *c*, *d*, *e*. The condition shown in fig. 6, *e* corresponds roughly to the adult venous drainage system.

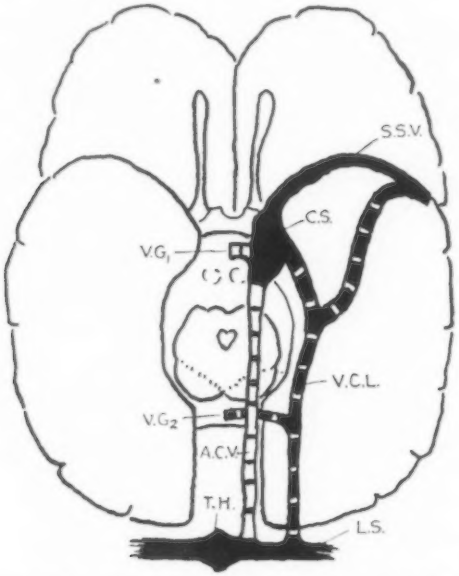


FIG. 7.—Vessels shown in continuous black are normally present in adult life. Dark interrupted lines indicate vessels that disappear during development normally but which have persisted in this case: light interrupted lines indicate fœtal vessels that have disappeared. A.C.V., anterior cardinal vein. C.S., cavernous sinus. L.S., lateral sinus. S.S.V., superficial Sylvian vein. T.H., torcula Herophili. V.C.L., vena capitis lateralis. V.G.1, vein of Galen—site during fœtal life. V.G.2, vein of Galen—site due to persistence of left vena capitis lateralis.

These details of development throw a definite light on the abnormal conditions present in the case which is described here. It is suggested that the large venous channel skirting the side of the mid-brain and joining anteriorly with the cavernous sinus is a persistent left vena capitis lateralis. Instead of draining straight into the lateral sinus and jugular bulb, it breaks up into a number of venous channels within the substance of the left occipital lobe. These re-assemble and then flow

into the lateral sinus by the vessel crossing the dural space. The large vessel lying in the Sylvian fissure is merely the dilated and distended counterpart of the normal superficial Sylvian vein; while the vessel joining the superficial Sylvian vein to the persistent vena capitis lateralis is a survival of the primitive superficial cerebral venous plexus found in that region.

The connection between the vein of Galen and the vessels at the base of the brain is usually lost. In this case, however, it has persisted. But with the growth backwards of the cerebral vesicles there is a tendency for the point of connection between the vein of Galen and the vessels at the base of the brain to be drawn backwards. This has apparently happened, the passage being made along the vessel that has persisted, i.e., the vena capitis lateralis. Thus a communication between the vein of Galen and the vena capitis lateralis is explained. A diagrammatic representation of this is shown in fig. 7.

The reason of the persistence of these venous channels is problematical. It is suggested that there is, in this case, an absence, or minimal development, of a capillary bed between the arterial and venous systems in the areas affected. The capillary bed acts as a buffer between those two systems, and the persistence and dilatation of these abnormal vessels is probably in the nature of a compensatory mechanism to deal with the abnormally large quantity of blood that is uncontrolled because of the absence of a "buffer" action of a capillary bed.

As to the classification of this lesion, it will be remembered that Ribbert [3] regards hæmangiomata as arising in rudiments of displaced fœtal tissue which are destined to form blood-vessels. From this rudiment they grow independently, thus explaining the apparent independence of the intra-hæmangiomatous circulation from the surrounding capillary circulation. In this case the vascular mass is dependent upon the normal circulation, and this fact in itself does not permit of its classification with the hæmangiomata.

Dandy has suggested the term "aneurysm by anastomosis" for such conditions, and this term not only fits this case, but also gives a very clear indication of the underlying pathological process.

It gives us great pleasure to acknowledge our indebtedness to Dr. M. A. MacConnaill of the Anatomy Department, The University, Sheffield, for his assistance with the embryological details in this case.

REFERENCES.

[1] Dandy. *Arch. Surg.*, 1928, **17**, 190.
[2] *Idem. Ibid.*, 1928, **17**, 715.
[3] Ribbert. *Virch. Arch.*, 1898, **15**, 381.

DIABETES INSIPIDUS.

BY ELIZABETH COWPER EAVES, M.D.,

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DIABETES INSIPIDUS is a comparatively rare condition; in a statistical examination Fitz found only fourteen cases per 100,000 patients. In the South Yorkshire Mental Hospital, which contains about 1,800 patients, many suffering with organic disease of the brain, one instance only has been recognized within the last six years.

The pathology of the condition is confusing. Many physiologists assume, owing to the properties of extracts of the posterior lobe of the pituitary and the undoubted fact that their administration has alleviated the symptoms in many reported cases, that the pituitary is necessarily involved. On the other hand, there is experimental and clinical evidence that a small lesion in the region of the tuber cinereum may bring about diabetes insipidus.

Polyuria may occur, but is not invariably associated, with tumours of the pituitary or in adjacent portions of the brain, and after cranial injuries, particularly fractures of the base of the skull. Syphilitic meningitis is an occasional cause. With or without obesity it may be a sequel of epidemic encephalitis.

The literature on the clinical and experimental aspect of diabetes insipidus is very large. Reference to much of this is given in papers by Kennaway and Mottram [10], Geiling [8], Bailey [2], Trendelenburg [13]. Little is known of the pathology of diabetes insipidus occurring in man, and in comparatively few instances has a complete examination been made both of the hypophysis and brain.

The first two cases to be described differ very widely from each other in their ætiology, Case 1 being probably due to a congenital defect and Case 2 being post-encephalitic.

CASE 1.—DIABETES INSIPIDUS WITH INFANTILISM.

A man, aged 21, a patient of Dr. Mathieson, suffered from epileptic fits from the age of 9. He was admitted to the South Yorkshire Mental Hospital two years before death. He had frequent severe epileptic fits, always appeared dazed and suffered greatly from headaches. His appetite was large, he was

always thirsty and he passed large quantities of urine. He was mentally defective, being unable to answer simple questions. The fits became progressively worse, and he finally died from exhaustion following numerous epileptic seizures.

He had had scarlet fever twelve months, and rheumatism eight years, before admission. His father is an epileptic.

Condition.—Although aged 21, he had the appearance of a boy of 10. He was very undersized, his weight being 5 st. and his height 4 ft. 9 in. The physical condition was rather similar to the Lorain type of infantilism. There appeared to be nothing unusual in the general appearance of the limbs. The head was large and contrasted with the small size of the face. The abdominal organs showed no abnormality. The testicles were very small.

No definite abnormality was detected in his nervous system. It was impossible to test sensation owing to his mental condition. Nothing abnormal was observed in the eyes. His pupils were equal and regular, and contracted directly and consensually to light and on accommodation.

The cardiac impulse was diffuse and a mitral systolic murmur was present. There was no arteriosclerosis. The urine had a specific gravity of 1005, and contained no abnormal constituents. Large quantities were passed.

Post-mortem examination.—The bones of the skull were unusually thick. The brain weighed 59 oz. The ventricles were normal. There was no excess of cerebrospinal fluid.

The pituitary.—The pituitary was not more than about half the normal size and of unusual form. In some parts it appeared to be constricted by connective tissue (plate VII, fig. 1). The cleft between the lobes seemed unusually wide considering the age, and was similar in this respect to that of a child. There was a cyst in the anterior lobe (fig. 2) and in the posterior lobe a partial division by a collection of small cells.

The cells of the anterior lobe were small and nearly all chromophobe. A few basophiles were found, but the number of acidophiles was extremely small, only 2·1 per sq. mm. in sections 4 μ thick.

The pars intermedia was also small; its cells were ill-formed and their cytoplasm scanty, in many cases the small nucleus almost filling the cell. In the pars nervosa the neuroglial cells were less than half the normal size, and the tissue seemed unusually vacuolated.

It seemed of interest to compare this pituitary with that in infantilism of a different type. Dr. S. J. Cowell kindly allowed the writer to examine the pituitary from a case of renal infantilism in a boy aged 16. This only weighed 0·34 grm., less than normal, but the acidophiles, although small and apparently few in number, averaged 700 to 900 per sq. mm., indicating a certain degree of activity.

The nervous system.—The most remarkable feature was the large size of the brain and its firm consistency. There was no obvious macroscopic abnormality, indeed it seemed a particularly well-developed brain, contrasting very much with the mental condition of the patient.

All parts of the central nervous system were examined microscopically. The main changes were those usually observed where the patient had died from status epilepticus, viz., chromatolysis of the nerve-cells and slight increase in the neuroglia. There was no degeneration of tracts, which appeared completely myelinated in Weigert-Pal preparations, and the various nuclei were very well developed. The medium-sized blood-vessels were slightly thicker than normal. In the hypothalamic region there were no lesions of any kind, apart from changes due to status epilepticus—similar to those in the rest of the nervous system. There was no destruction of nerve-cells in the substantia nigra nor in any other part of the mid-brain.

Although histologically the brain appeared to be well developed, it was thought that chemical analysis might reveal some abnormality. The amount of phosphorus was remarkably low, being only 0·204 grm. (expressed as P_2O_5) in 100 grm. of cerebral cortex. The amount of phosphorus varies normally from 0·35 to 0·4 grm. The amount of calcium was probably within normal limits—4·8 mg. per 100 grm. of cerebral cortex.

Case 2.—Post-Encephalitic Diabetes Insipidus.

A man, aged 29 at death, was admitted to Lodge Moor Hospital in 1924 under the care of Dr. A. G. Yates, with acute epidemic encephalitis. He recovered and was discharged. Subsequently, he began to complain of mental depression, had outbursts of temper, could take no interest in anything and had thoughts of suicide. Early in 1926 he complained of thirst and headache and began to get fat. Exact weights are not available, but he very obviously put on a great deal of weight and drank enormous quantities. In April, 1926, he was admitted to the Firvale Infirmary Mental Ward. He was then mentally degenerated, slept a great deal, and had frequent epileptiform attacks in which he was unconscious, bit his tongue and was incontinent. There was a faint trace of Parkinsonism, but this never became at all marked. Epileptic fits and polydipsia continued until August 15, 1926, when he died suddenly in an epileptic seizure.

The quantity of urine was always very large—in one day 178 oz. (about 5,038 c.c.), another time 6,800 c.c. Its specific gravity was 1005, but it contained no abnormal constituents.

The pupils reacted to light, but the left was larger than the right. The abdominal and plantar reflexes were normal. The Wassermann reaction was negative.

Post-mortem.—The stomach was enormously dilated, but all the other organs appeared normal, including the kidneys.

The pituitary.—The pituitary was larger than normal. It weighed 0·75 grm. On making a vertical antero-posterior section, a collection of colloid could be seen between the anterior and posterior lobes (fig. 3).

Microscopically, in the anterior lobe the acidophiles seemed fairly abundant but slightly smaller than usual, and there were islands of hyperplasia. The basophiles were fairly numerous in some areas.

In the pars intermedia there were numerous vesicles or cysts of varying sizes containing colloid, some of which possessed a definite cellular wall. In one large vesicle the lining cells appeared to be ciliated. There were also many islands of cells enclosed by connective tissue which occasionally contained colloid towards the centre. There appeared to be here some hyperplasia of the pars intermedia. Some of the cells were vacuolated and more chromophobe than normal. The colloid varied in its staining properties, for example with Mallory's aniline blue-orange G part of it stained yellow, part blue, signifying some difference in reaction.

In the pars nervosa the neuroglial cells and fibres seemed well developed. Clumps of bright yellow pigment were abundant, also ill-defined feebly staining colloid masses at intervals. There was a tendency to accumulation of hyaline material round the vessels. In some areas the neuroglial fibres were unusually widely separated as though there had been some distension by secretion.

The nervous system.—There was no wasting of the brain, which weighed 48 oz.

There was no percentage diminution of phosphorus compounds as is invariably found in degenerative conditions of the nervous system, such as general paralysis of the insane and in Huntington's chorea (0·405 P_2O_5 in 100 grm. of cerebral cortex). Chemical analysis indicated an increased calcium content. In the frontal cortex the amount was 9·8 mg. in 100 grm., the average figure at the age of the patient being from 4 to 4·5 mg. In other regions than the cortex, as in the hypothalamic region and throughout the brain-stem, there was even greater increase in calcium if one could judge by the histological appearance.

All parts of the nervous system were examined histologically, and as far as possible serial sections of the hypothalamic region were made. The most striking feature was the condition of the blood-vessels. These were thickened, and spaces existed round them. This was not due to fixation, which was otherwise fair. Hæmorrhages were not frequent, but a small one was found in the hypothalamic region immediately anterior to the corpus mammillare; it did not involve any nucleus of nerve-cells.

There was no obvious degeneration of tracts in Weigert-Pal preparations. Chromatolysis of nerve-cells and neuronophagia were present throughout the whole nervous system, but it was remarkable that these changes were notably less than in most of the nine other cases of chronic epidemic encephalitis that I have examined.

In the hypothalamic region all the nerve-cells exhibited chromatolysis, and some were in process of destruction and surrounded by glia cells (fig. 4.) As particular importance has been ascribed to a lesion of the ventral nucleus as a causative factor in the production of polyuria (Camus and Roussy [4], Bailey and Bremer [3]), an attempt was made to compare the amount of change in the nerve-cells of this nucleus with that in the periventricular nuclei, the nuclei of the optic tracts, the accessory supra-optic nuclei and the corpora mammillaria, but it was found to be impossible.

In the substantia nigra many nerve-cells remained, although few could be considered normal. Contrasting these findings with those in nine other brains from cases of epidemic encephalitis in which there was no diabetes insipidus, it is to be emphasized that in some of the latter the destruction of cells in the hypothalamic region was so great that the different nuclei could not always even be identified, and in some of these brains the ventral nucleus of the tuber appeared to have suffered more than the other nuclei. In the majority of cases only small clumps of pigment remained in the substantia nigra to mark the original site of the cells of this structure.

The liver, in spite of the obesity, contained no stainable fat and appeared otherwise normal, except for a slight increase of tissue around the portal canals. Owing to post-mortem changes in the pancreas, no statement can be made about it.

CASE 3.—TRANSITORY POST-ENCEPHALITIC DIABETES INSIPIDUS.

G. C., a man aged 17 at the outset of his illness, a patient of Professor Hall at the Sheffield Royal Hospital, had epidemic encephalitis in January, 1922, when he was very drowsy for eight or nine weeks. In May, 1925, polydipsia and polyuria developed, the specific gravity of the urine being then about 1002 and the total daily amount about ten litres. He was treated with pituitrin by Dr. Imrie, with the result that the polyuria decreased (Tingle and Imrie [12]). By August, 1926, thirst and polyuria had disappeared, but tremors, rigidity and oculogyric crises were present. He continued to lose weight. He became bad-tempered and violent occasionally.

When examined in June, 1929, he was markedly Parkinsonian, helpless and very thin. He was usually quiet and orderly, but at intervals he was difficult to manage. The patient said he had terrible attacks in which his eyes turn up. These attacks were stated by the Charge Nurse to last sometimes as long as two days. He was not now troubled by excessive thirst.

The fundi appeared normal. The pupils reacted sluggishly to light. There was paresis of the right external rectus muscle and bilateral weakness of the facial muscles, more marked on the right side. Nothing abnormal was observed in the other cranial nerves. The right pupil dilated more to shade than the left. Sweating was considerable. Tremors were present in the ocular muscles, tongue, lips and in the limbs, and there was great rigidity. The specific gravity of the urine varied between 1012 and 1018. It contained no albumin nor sugar. The total quantity in twenty-four hours was about 60 oz. (1,698 c.c.).

CASE 4.—TRANSITORY DIABETES INSIPIDUS WITHOUT NERVOUS DISEASE.

Mrs. C., a woman aged 29, under the care of Professor Hall, was admitted to the Sheffield Royal Hospital in July 1908, suffering from great thirst and polyuria. These symptoms dated from the birth of her ninth child three months previously. During the three weeks in hospital the average daily amount of urine was 3,500 c.c. The specific gravity varied from 1003 to 1006,

and there were no abnormal constituents. In September, 1915, she seemed much better, but still had abnormal thirst: for example, she would usually drink about a quart of water in the night. In February, 1929, more than twenty years after the onset of diabetes insipidus, she was quite well, and no longer had either polydipsia or polyuria. The specific gravity of the urine was about 1015.

Some Abnormalities of the Posterior Lobe of the Pituitary without Polyuria.

(*a*) *Hyperplasia of the pars intermedia and of the pars tuberalis.*—The appearances, seen in the posterior lobe of the pituitary in a case of acromegaly under Professor Hall at the Sheffield Royal Hospital, seem of some importance. The patient had never been known to have diabetes insipidus. This pituitary weighed 2·4 grm. In addition to the usual hyperplasia of the pars anterior, there was also a hyperplasia of the pars intermedia, such as the present writer has not previously seen in any pituitary. The pars nervosa was very small, but the pars tuberalis seemed unusually large.

Hyperplasia of the pars intermedia was also found in a pituitary from a case of epidemic encephalitis in which polyuria had not been present. This differed from Case 2, in that in the latter the pars intermedia was divided into islands by increased connective tissue.

(*b*) *A tumour involving the pars nervosa.*—This was a case of Dr. E. F Skinner in which a pituitary tumour had not been suspected. Macroscopically, the whole posterior lobe appeared to be involved by a tumour which extended round both sides of the pituitary. Microscopically, however, the pars nervosa alone was found affected, the pars intermedia being to some extent hyperplastic.

Discussion.

There are two main theories advanced to explain diabetes insipidus.

(*a*) *The endocrine theory.*—Posterior lobe extract has both a diuretic and anti-diuretic effect, and consequently there are two variations of this theory: (1) that polyuria is due to an increased secretion of hormone; (2) that it is brought about by a diminution in the available amount of hormone either owing to a deficient production or interference with absorption. The balance of evidence is that the effect of posterior lobe extract is mainly anti-diuretic in human beings. The site of origin of an active extract is probably the pars intermedia rather than the pars nervosa. It has been shown earlier that neither hyperplasia of the pars intermedia nor of the pars tuberalis is associated with polyuria.

(*b*) *The nervous theory*, as propounded by some workers, excludes the pituitary from any share in the production of polyuria and ascribes the condition to lesions in the hypothalamic region [2], [3], [4].

A reconciliation of the two theories is possible. That there are actually nerve-fibres in the pituitary, except to the vessels, has been disputed owing to technical difficulties in their demonstration. M. M. Croll [6], however, has recently shown beyond doubt that in the rabbit the pars intermedia is very richly innervated (the references to previous work are given in her paper), and Greving [9] and Pines [11] have described tracts of fibres passing from the hypothalamic region to the hypophysis. A disturbance of function of the pituitary by interference with the nerve supply is therefore a possibility.

In Case 1 there was no definite lesion of the nervous system to account either for diabetes insipidus or for infantilism. Some workers, more particularly of the French school, have ascribed infantilism also to lesions in the hypothalamic region. The histological findings in the brain resembled those in other cases of macrocephaly (Anton [1] and Wigglesworth and Watson [14]), that is, there were few or no pathological changes apart from those usually found in epilepsy. There was no tumour of the pituitary to exert pressure on adjacent nerve-centres, but the pituitary was maldeveloped and there was histological evidence of under-activity, at any rate of the anterior lobe. The polyuria in this case must, therefore, be considered to be due to insufficient production of hormone by the pituitary.

In Case 2 the pituitary in no way resembles that in Case 1, as it was slightly larger than normal, and there was hyperplasia of the pars intermedia. Polyuria was not due to this hyperplasia, as will be obvious from a comparison with the acromegalic pituitary. Comparing this pituitary from Case 2 with those from other cases of epidemic encephalitis, the most important difference was the presence of a larger amount of colloid in the pars intermedia than in any of the others except one from encephalitis with obesity. There was the possibility of interference with absorption of hormone into the blood-vessels owing to their abnormal condition, and into the third ventricle owing to the increased calcium in the brain.

The mildness of the lesion in the hypothalamic region in Case 2, compared to the severity of the changes in other encephalitic brains, is in line with the clinical condition of Case 3 at different stages of the malady. In both Cases 2 and 3, diabetes insipidus occurred before the onset of definite Parkinsonism. The disappearance of polyuria in Case 3 was obviously not due to improvement of the condition of the nervous system, the changes in which were progressive. It may be attributed to the use of pituitrin, but although this substance had an

immediate effect while it was administered, the effect was hardly likely to be permanent when it was withdrawn.

Transitory diabetes insipidus, with progressive disease in the nervous system, has been noted by Fulton and Bailey [7] in two cases. In one of these polyuria had been present for five or six years, but disappeared eight months before death. The tuber cinereum was involved by a tumour, and there was dense gliosis and only a few sparse surviving neurons. The hypophysis was normal.

In any consideration of the influence of the nervous system on the pituitary, it is generally assumed that if there is nervous control stimulation of a particular group of nerve-cells will bring about secretion. But the effect may be of an inhibitory rather than a secretory nature, and a mild lesion by stimulating such a centre may inhibit the secretion of the anti-diuretic hormone. That a ductless gland may be influenced by inhibitory impulses from the nervous system has been shown in the case of the islets of Langerhans of the pancreas by Clark [5].

Case 4 illustrates that transitory diabetes insipidus is not necessarily a symptom of a serious and progressive disease. There were never any neurological signs, and the condition followed pregnancy where there is even normally some alteration in the function of the pituitary.

Conclusions.

(*a*) Diabetes insipidus may be due to a transient affection of the pituitary, and this gland may recover its function completely.

(*b*) It may be present as a permanent condition owing to a more severe affection of the pituitary—as, for example, a congenital defect.

(*c*) Neither hyperplasia of the pars intermedia nor of the pars tuberalis of the pituitary causes diabetes insipidus.

(*d*) A relatively mild lesion in the hypothalamic region of the brain may bring about diabetes insipidus. It is suggested that this is due to stimulation of an inhibitory centre or tract to the pituitary, thus causing inhibition of secretion of the posterior lobe hormone.

(*e*) A severe lesion in the hypothalamic region of the brain—in contradistinction to a milder one—does not bring about diabetes insipidus—as was apparent in nine cases of chronic epidemic encephalitis.

The writer is indebted to Professor Hall for particulars of two of his cases and for the pituitary from his case of acromegaly; to Dr. A.

PLATE VII.

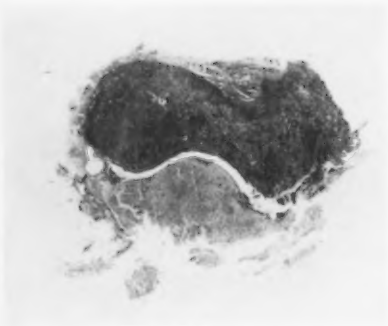

FIG. 1.

FIG. 2.

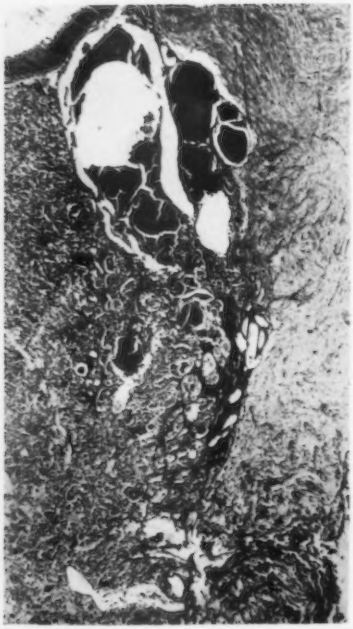

FIG. 3.

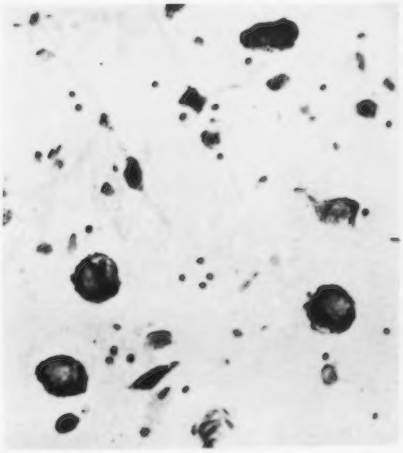

FIG. 4.

To illustrate article by Elizabeth Cowper Eaves.

G. Yates for permission to publish his case of post-encephalitic diabetes insipidus; and to Professor Leathes for some helpful criticism. She thanks Mr. C. Stewart and Mr. R. Stewart for assistance with photomicrography.

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DESCRIPTION OF PHOTOMICROGRAPHS. Plate VII.

Fig. 1.—*Case* 1. Pituitary. × 5½. Antero-posterior section. The pituitary is of abnormal form and is constricted in one place by connective tissue. The cleft between the lobes is unusually patent for the age.

Fig. 2.—*Case* 1. The pituitary at the junction of the anterior and posterior lobes. × 17½. There is a cyst containing degenerative material in the pars anterior, and the pars nervosa is partly divided by small cells.

Fig. 3.—*Case* 2. Antero-posterior vertical section of the pituitary. × 18. (Fuchsin and Mallory's aniline blue orange G.) Large vesicles containing colloid. The amount of connective tissue at the junction of the two lobes is increased and divides up the slightly hyperplastic pars intermedia into islands.

Fig. 4.—*Case* 2. Nerve-cells in the hypothalamic region. × 280. The nucleus of the cells is eccentric in position. The centre of the cells contains no Nissl granules, the edges stain darkly with methylene-blue. Some of the cells are being destroyed.

THE PITUITARY AND HYPOTHALAMIC REGION IN CHRONIC EPIDEMIC ENCEPHALITIS.

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AND

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IT is well known that in epidemic encephalitis symptoms occasionally occur similar to those which have been attributed to affections of the pituitary or to lesions in the hypothalamic region of the brain. Obesity, sometimes approximating to Fröhlich's type, and diabetes insipidus, are the two more common of the symptoms with a debatable hypophyseal or nervous origin, but hypophyseal infantilism and acromegaly have been also described, but they are very rare.

Obesity, or some unusual increase in weight, seems to be commoner than diabetes insipidus, though the two symptoms may be present in the same case. Exact statistics as to the actual proportion of cases which have diabetes insipidus do not seem to be available but a review of the literature makes it evident that this rare condition occurs with greater frequency in epidemic encephalitis than in any other disease. There is considerable variation in the percentage figures given by different observers with regard to the number of cases in which there is obesity. For instance, Grossman [8] who examined a series of eighty-nine cases, mainly children, found it in 15 per cent.; Duncan in a series of eighty-three cases in about 8 per cent. Professor Hall tells us that these figures are higher than he has found. A number of instances of post-encephalitic obesity are cited in the monographs by A. J. Hall [9] and F. Stern [16].

The occurrence of post-encephalitic infantilism and acromegaly—although we have only found one example of each in the literature—is of great interest because the pituitary must have been affected. Bremer [3] observed acromegaly to develop quickly after a typical attack of epidemic encephalitis, and Parhon, Ballif and Märza [15] have described a case of post-encephalitic infantilism with diabetes insipidus.

Many patients with chronic epidemic encephalitis become very wasted, but the reason for this emaciation is not obvious. A variety of Parkinsonism, accompanied by severe wasting, has been described, but the two conditions are not necessarily associated as will be seen from a consideration of some of the ten cases described in this paper. It seems, therefore, worth considering if this cachexia is due to any change in the pituitary.

Disturbances of sleep are present in practically all cases of epidemic encephalitis at some time. The possibility that pathological drowsiness is due to hypofunction of the pituitary must be considered. It is common knowledge that lesions in the hypothalamic region may cause disturbances of sleep, and it is usually assumed that this is the cause in epidemic encephalitis without, however, there being definite proof.

Our attention was first attracted to the problem of the pituitary and the hypothalamic region in epidemic encephalitis because of the opportunity afforded to one of us to examine the pituitary and nervous system in a case of post-encephalitic diabetes insipidus. It was realized that in such a diffuse disease as epidemic encephalitis the fact that any definite pathological change was present in the pituitary or hypothalamic region did not necessarily indicate that these changes were responsible for any particular symptoms; and it seemed necessary to compare the appearances in this case of diabetes insipidus with those of the same structures in the brain of other cases of epidemic encephalitis in which this symptom was absent. It was also important to ascertain with what frequency and severity changes might exist in the hypothalamic region in the absence of any syndrome commonly attributed to a lesion in this area.

Previous Work on the Pituitary and Hypothalamic Region in Epidemic Encephalitis.

The paucity of pathological data is in rather striking contrast with the number of clinical instances of post-encephalitic hypophyseal syndromes. The pituitary has occasionally been examined in acute cases of short duration. Marie and Trétiakoff [13], who comment on the absence of information about the hypophysis in epidemic encephalitis, examined this structure in two acute cases in which drowsiness was a prominent symptom. They noted congestion but no pathological change which was not found in other conditions. Apparently the hypothalamic region was not examined.

Howe [11] described some pathological changes in four acute cases,

and states that while the alterations in the pituitary are definite, there is no evidence that the course of the disease is influenced thereby. He considers, however, that many more cases should be investigated before definite conclusions are reached.

G. Levy [12] found the hypophysis normal in four instances where apparently there were no clinical signs suggestive of pituitary involvement.

Parhon, Ballif and Mârza [15] made a clinical and anatomical study of a case of post-encephalitic diabetes insipidus and infantilism. They attributed these conditions to changes in the hypothalamic region, and considered the hypophysis normal, but this seems questionable in view of their description. Urechia and Elekes [18] found changes in the tuber cinereum in three cases of epidemic encephalitis, but they do not give a detailed account of the hypophysis.

Stief [17], who mentions that anatomical findings in the hypothalamus have seldom been recorded, gives a short description of them in one case of epidemic encephalitis, and also describes various changes in the hypothalamic region in general paralysis and in arteriosclerotic disease.

On reviewing the work that has been done on the hypothalamic region in epidemic encephalitis, it is noteworthy that few workers have endeavoured to study a series of cases with a view to correlating the changes with clinical symptoms as has been done, for example, to a considerable extent in the case of the substantia nigra. It is easy to ascertain the degree of destruction in the latter structure owing to its compact form and the residual melanin pigment which is found even after the total disappearance of the cells. In the hypothalamic region owing to the more diffuse arrangement of some of the nerve-cells and the fact that there is not necessarily anything to mark the site of their disappearance, it is much more difficult to classify the changes as slight, moderate or severe, unless a number of brains are examined. We experienced this difficulty when we first began this investigation, and the final conclusions as to the significance of the alterations in the brain from a case of diabetes insipidus would have been quite different if this had been the only one examined.

The Hypothalamic Region of the Brain.

The nuclei of this region of the brain have been variously described by different authorities; and in lower animals, such as the dog, they do not always correspond with those in the human brain. We have

followed the nomenclature of Foix and Nicolesco [7]. Figure 1, which is an outline of an actual section, gives an indication of the extent of the hypothalamic area examined in this investigation. The nuclei are represented diagrammatically.

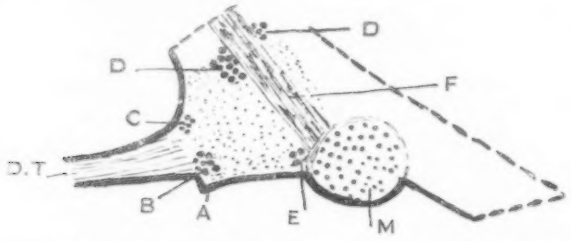

FIG. 1.—Hypothalamus. Outline of actual section (× 2½). Nuclei represented diagrammatically. O.T., Optic tract. A, Place of attachment of pituitary stalk. B, Ventral nucleus. C, Nucleus of the optic tract. D, Periventricular nucleus. E, Magnocellular nucleus. F, Anterior pillar of the trigone. M, Corpus mammillare. The diffuse parvocellular nucleus extends over the whole infundibular region.

TEN CASES OF CHRONIC EPIDEMIC ENCEPHALITIS.

Nine cases were patients in the South Yorkshire Mental Hospital. In three (Cases 3, 5 and 9) the initial illness was slight or was not diagnosed until the development of Parkinsonism some time later. The duration of the disease in the ten cases varied from two to five years. Five of the ten patients died from the disease, two died from erysipelas of short duration, one from malaria used as an experimental therapeutic measure, one from chronic tuberculosis, and one from influenza and bronchopneumonia.

HISTOLOGICAL METHODS USED FOR THE EXAMINATION OF THE PITUITARY AND NERVOUS SYSTEM.

Pituitary.—After a preliminary short fixation in 10 per cent. formalin the pituitary was cut in half by an antero-posterior vertical section. A portion of the formalin fixed material was saved for frozen sections. The rest was fixed in Regaud's solution, and serial paraffin sections were made of it. The staining methods were as follows :—

(*a*) Weigert's iron hæmatoxylin and azo-eosin.

(*b*) Weigert's iron hæmatoxylin and Biebrich scarlet.

(*c*) Mallory's aniline-blue orange G with and without acid fuchsin. This method was useful owing to the difficulty of staining colloid and hyaline masses when present in the posterior lobe.

(*d*) A portion of the pituitary was embedded in gelatine and the formalized block cut frozen. The sections were examined for pigment and stained for fat with Scharlach R.

As it has been stated that post-mortem changes occur readily, we have examined several normal human and animal pituitaries, one piece being fixed immediately and other pieces fixed at varying intervals up to a period of forty-eight hours: we found only slight changes, no apparent alteration taking place in twenty-four hours, but in forty-eight hours slight vacuolation of some of the cells was discernible.

The nervous system.—Nearly all parts of the nervous system have been examined but are not here described in detail. Fixation was carried out in 10 per cent. formalin, and sections were mordanted in potassium bichromate when necessary.

The hypothalamic region.—Usually half was embedded in paraffin and the other half in celloidin, vertical sagittal sections being made and cut serially as far as possible.

For paraffin sections the methods used were:—

(*a*) Polychrome methylene-blue and alcoholic eosin.

(*b*) Methylene-blue and carbol-fuchsin, the latter being useful for the demonstration of increased pigment.

(*c*) Mallory's aniline-blue orange G with and without acid fuchsin.

For the celloidin sections the methods used were:—

(*d*) Weigert-Pal preparations, sometimes counterstained with alum carmine.

(*e*) Mallory's phosphotungstic acid and hæmatoxylin followed by differentiation in a 30 per cent. solution of ferric chloride.

(*f*) Frozen sections were sometimes used for the demonstration of neuroglia, the method being methyl violet preceded by Anderson's mordant.

In the description of the nervous system other than the hypothalamic region, emphasis is laid more especially on the condition of the cells of the substantia nigra, for as the degree of destruction of this area is readily ascertainable, it affords some standard of comparison.

CASE 1.—POST-ENCEPHALITIC DIABETES INSIPIDUS WITH OBESITY.

This case has been previously described in an account of diabetes insipidus (see p. 47).

CASE 2.—EARLY TRANSIENT NARCOLEPSY AND LATE CACHEXIA.

G. E. R., a man, aged 50 at death, had epidemic encephalitis in March, 1924, his first symptom being diplopia. He used to fall asleep suddenly in

the street, and for this came into contact with the police. He became very depressed and was admitted to the South Yorkshire Mental Hospital in January, 1925. He then complained constantly of headache, of feeling cold of obscure abdominal sensations and of inability to sleep. In June, 1925, he had two epileptic fits, but none were noted afterwards. In December, 1925, he was in a typical Parkinsonian state. His intelligence remained good, but he continued to sleep badly and lost weight (about 2 st. in 1926). His urine contained no abnormal constituents, its specific gravity was 1015 in January, 1925, and 1020 in March, 1927. His general condition deteriorated and he finally died from the disease in December, 1927.

The pituitary seemed rather small. The pars anterior was congested and there was vacuolation of the cells, and in some of them there was a clear ring round the nucleus, particularly in the acidophiles.

Neither the pars intermedia nor pars nervosa showed unusual features except that in the latter there was a greater amount of pigment than normally. The small portion of the pars tuberalis around the stalk seemed normal. There were no globules of fat in any part of the pituitary.

The nervous system.—The brain weighed 46 oz. and there was perhaps some general wasting. This certainly was so in the hypothalamic region, and the brain-stem seemed unusually small. The third and one lateral ventricle were dilated.

There was no obvious tract degeneration apparent in Weigert-Pal preparations.

The mid-brain.—There was great destruction of nerve-cells, especially in the substantia nigra in which there was practically total disappearance of nerve-cells and increase of neuroglia. Around most of the blood-vessels there were numbers of small round cells, producing a cuffing which is more common in acute than chronic epidemic encephalitis.

The hypothalamic region.—In the corpus mammillare the nerve-cells exhibited chromatolysis. Many were vacuolated and contained pigment, but on the whole this structure was less affected than the other nuclei of this region. The cells of the magnocellular nucleus seemed to be fewer in number than normal, those remaining being in process of destruction, and the same was true of the periventricular nucleus. In the ventral nucleus of the tuber and the nucleus of the optic tracts, the changes were more intense and these nuclei could only be identified with difficulty as most of the cells had lost the greater part of their cytoplasm. Several hæmorrhages were found in the hypothalamic region, but these were not common elsewhere.

Case 3.—Pathological Drowsiness and Cachexia.

M. M., a woman, aged 53 at death, was admitted in March, 1926, to the South Yorkshire Mental Hospital, the diagnosis being melancholia. She complained of depression and of inability to sleep owing to this. She had had influenza in 1924, and another severe attack just before admission. She stated later that on the second attack she had double vision. Epidemic encephalitis

was not suspected at first. The only neurological sign present on the patient's admission to hospital was inequality and sluggish reactions of the pupils. The Wasserman reaction was negative. She complained at intervals of unusual feelings in the limbs. By December, 1926, she had become definitely Parkinsonian. She became progressively worse. From the beginning of 1928, she seemed to sleep all the time; she could be roused to answer questions, but immediately afterwards fell asleep again. A kyphosis developed and trophic changes were present. Her urine was normal. She became very emaciated, and died in September, 1928.

The exact amount of weight lost is not known, but she weighed only 5 st. 11 lb. a few months before death.

The pituitary.—The pars anterior was congested and immediately underneath the capsule were two hæmorrhages which extended into its substance, destroying two small areas. In the centre of the hæmorrhage isolated disintegrating cells could be seen. The pars anterior of this pituitary was more damaged than any other in the series. Most of the cells had either lost their cytoplasm or were very vacuolated (fig. 4.) Some of the remaining acidophiles had a swollen appearance. There were small areas with numerous nuclei but with the cytoplasm of the cells destroyed. This was probably originally an attempt at repair. Vesicles containing colloid and resembling the thyroid were common in the pars anterior. The cells in the portion of the pars tuberalis around the stalk were very vacuolated and many had lost all their cytoplasm.

There was a moderate amount of colloid in the pars intermedia, the cells of which invaded the pars nervosa, which was very congested. No fat globules stained by Scharlach R. in the pituitary, but fine pigment granules with some affinity for this dye were observed in the cells of the pars anterior.

The nervous system.—The brain weighed 44 oz. Some wasting was apparent in the hypothalamic region and in the right post-central area of the cerebral cortex. The brain was rather chocolate coloured and seemed firmer than normal. The Sylvian aqueduct and third ventricle were slightly dilated.

There were extensive changes throughout the whole nervous system, greater than in any other brain in this series. These changes were at a maximum in the mid-brain and hypothalamic region.

The nervous system stained fairly well by the Weigert-Pal method, but there was some tract degeneration in the lateral columns of the spinal cord and in the medulla.

The mid-brain.—The cells of the substantia nigra had disappeared as in Case 2. Many fibres were obviously abnormal, as they presented varicosities and constrictions, the appearance being similar to the "beaded" effect observed by McAlpine in the substantia nigra in other cases. This was present in other parts of the nervous system but to a much less extent, except in the hypothalamic region where it was also a characteristic feature.

The hypothalamic region.—The cells of the corpus mamillare were diminished in number, contained no Nissl granules, and many were completely filled with pigment. The cells of the magnocellular nucleus were swollen and stained a

dull red in methylene-blue and eosin preparations. In the part of the periventricular nucleus posterior to the anterior pillar of the trigone there was a hæmorrhage, and only a few cells remained. In the anterior part of this nucleus all the cells were abnormal, being either filled with pigment or staining abnormally. In the ventral nucleus of the tuber the destructive changes were still greater, and there was an old hæmorrhage about the site of the nucleus of the optic tract.

The increase of neuroglial cells and fibres was not sufficient to compensate for the destructive processes, as this area showed the condition "status spongiosus," described by Spielmeyer in other conditions, in different parts of the nervous system (fig. 7). There was practically no cuffing of the blood-vessels, but occasionally there were cells outside the vessels, more commonly plasma than round cells. Hæmorrhages were very numerous; in the hypothalamic region, in addition to those already mentioned, there were several other old and recent ones (fig. 6). The age of the hæmorrhage was indicated to some extent by the amount of increase of neuroglia around it, and also by disintegrating masses of pigment. Similar hæmorrhages were present in the mid-brain, in the nuclei of the ninth and tenth nerves, and in the spinal cord.

Case 4.—Post-Encephalitic Mania, Epileptiform Attacks and Sudden Death.

D. F. B., a girl, aged 18 at death, had epidemic encephalitis in March, 1924, when she had diplopia, occupation delirium, and drowsiness. She complained later of insomnia, but on the whole she remained drowsy. By May, 1926, she had become slower in her movements, rigidity was present on the right side and myotonia in the right hand. She began to have "dizzy" bouts, in which she would fall. In September, 1926, tremors were troublesome, and she usually then slept heavily in the morning. By August, 1927, she was occasionally excitable and had epileptiform attacks. After an attempt at suicide prompted by auditory hallucinations she was admitted to the South Yorkshire Mental Hospital in October, 1927. She became impulsive and dangerous. In April, 1928, she was placed one day in a side room owing to previous excitement, and she was found dead an hour later.

There was no noticeable alteration in weight during the patient's stay in the South Yorkshire Mental Hospital.

The pituitary was of average size (0·6 grm.). It was very congested. In the pars anterior there were two or three irregular-shaped masses of colloid material containing remains of cells, but the majority of the cells were well formed and the relative number of chromophile cells was within normal limits. There was a slight increase of connective tissue. The cleft between the lobes was unusually patent and contained a small amount of colloid material. The posterior lobe showed nothing unusual. There was no fat stainable by Scharlach R. in any part of the pituitary.

The nervous system.—The brain weighed 43 oz. and there was no wasting.

It was very congested, but compared to some of the other brains in the series the histological changes in many areas were comparatively slight. There was no obvious tract degeneration in Weigert-Pal preparations.

The mid-brain.—In the substantia nigra the nerve-cells were very little altered compared to the rest of the series except those in Case 1, and no difference was observed in the cells of the two sides (rigidity had existed mainly on one side).

In the hypothalamic region the alterations in the nerve-cells were less than in Cases 2 and 3. The cells contained an unusual amount of pigment considering the age of the patient, and there was a spongy condition in some areas, as in Case 3. This was not due to the fixation, which was good in the rest of the nervous system. The corpus mammillare showed only comparatively slight alterations except that a small mass of pigment in its posterior part indicated an old hæmorrhage. Some of the cells of the magnocellular nucleus and many of the periventricular nucleus were intact. In the anterior part of the latter structure there was a small hæmorrhage and a large one immediately anterior (fig. 7). In the ventral nucleus many cells were vacuolated, but there was less alteration than in the nucleus of the optic tracts. Multiple hæmorrhages were a characteristic feature in both the hypothalamic region and mid-brain, though none were observed in the cerebral cortex nor in the pons and medulla.

Calcium content.—Although the cerebral cortex was comparatively normal histologically, there were noteworthy alterations in its calcium content. This amounted to 9·5 mg. calcium in 100 grm. of cortex as compared to an average of 4 to 4·5 mg. at this age. As far as could be judged from histological appearances there was even greater increase of calcium salts in the hypothalamic region.

No changes were found in other organs of the body.

Case 5.—Cachexia.

W. B., a man, aged 52, was admitted to the South Yorkshire Mental Hospital about two years before death, with a provisional diagnosis of confusional insanity. Some months later he was noticed to be apathetic and drowsy and began to develop Parkinsonism. A diagnosis of epidemic encephalitis was then made. The Parkinsonian condition was extreme and the patient was wasted at the time of his death from this disease, about eighteen months later.

The pituitary.—This weighed 0·7 grm.—slightly greater than the normal weight. Some congestion was present. In the pars anterior the majority of the cells were acidophiles, small in size and with darkly staining nuclei. The cells were not otherwise abnormal. There appeared to be hyperplasia, particularly of the pars anterior (fig. 3) but also to a slight extent in the pars intermedia, in which there was an average amount of colloid arranged in vesicles. The pars nervosa showed nothing unusual.

The nervous system.—The brain weighed 45 oz. A description of

the nervous system, with the exception of the hypothalamic region, which unfortunately was not available for examination, has been already published [5].

Case 6.—No Alteration in Weight.

A. N., a man, aged 28 at death, had epidemic encephalitis in May, 1924. After an attempt at suicide he was admitted to the South Yorkshire Mental Hospital in September, 1925. He was then very depressed, complained of not sleeping at night and of pains in his arms. He was in an advanced Parkinsonian state. He constantly complained of pains in the arms and shoulders. In September, 1927, he developed erysipelas and died seven days later.

In September, 1925, his weight was 10 st. 6 lb. (height 6 ft.), and in September, 1927, 10 st. 9 lb. There was no abnormality in the urine, the specific gravity of which was 1022.

The pituitary.—The pars anterior was congested, especially the vessels at the junction of the two lobes. The cells were mainly acidophiles and slight hyperplasia was present. The pars intermedia and pars nervosa appeared normal except for some increase of connective tissue at the junction.

The nervous system.—The weight of the brain was not known, but it seemed unusually small. There were changes throughout the nervous system, most marked in the mid-brain. Some degeneration of the lateral columns of the medulla was apparent in Weigert-Pal preparations.

The mid-brain.—The walls of the blood-vessels were thickened. In the substantia nigra there was considerable destruction of nerve-cells.

The hypothalamic region.—There were pathological changes in the nerve-cells, but the appearances in the different nuclei are not described, as such lesions may be brought about by a high temperature. In Weigert-Pal preparations the nerve-fibres were altered and, as in Case 3, presented a beaded appearance, and there was increase of neuroglial fibres in the tuber cinereum. The latter changes must be attributed to epidemic encephalitis.

Case 7.—Post-Encephalitic Obesity.

G. F. G., a man, aged 31 at death, had an attack of "influenza" in December, 1925, and had double vision occasionally. He became very depressed and on admission to the South Yorkshire Mental Hospital in July, 1926, he was in a Parkinsonian state and unable to walk. He had occasional epileptic fits, but had been subject to epilepsy since the age of 19.

His weight increased progressively from 7 st. 8 lb. in July, 1926, to 10 st. 7 lb. in September, 1927.

He died in February, 1928, two days after contracting erysipelas.

The pituitary.—A large amount of colloid could be seen between the anterior and posterior lobes. The pituitary was of rather unusual form, being elongated in an antero-posterior direction. The anterior lobe was congested, a

fair number of acidophiles was present, but the cells were unusually discrete. The large mass of colloid showed variations in its staining properties in different areas. At the junction of the pars intermedia and pars nervosa and in the latter, was a group of cells rather similar to mucous acini. Possibly these had nothing to do with the encephalitic condition, as a similar appearance has been seen by the writers in the case of another epileptic. The fibres of the pars nervosa were unusually widely separated.

The nervous system.—The brain weighed 49 oz. and there was no apparent wasting.

The mid-brain.—The substantia nigra was very severely damaged, most of its cells being destroyed.

The hypothalamic region.—Although all the nerve-cells were more or less abnormal, there was less destruction than in some of the cases (e.g., 2 and 3); the different nuclei could be recognized, but as all were affected it is difficult to make comparisons.

In the corpus mammillare the number of nerve-cells appeared fewer and more abnormal than in Case 1. The magnocellular and periventricular nuclei were comparatively little altered. In the ventral nucleus of the tuber there were fewer cells than normal. There were two small hæmorrhages in the hypothalamic region, probably of recent origin. One was immediately anterior to the corpus mammillare.

Case 8.

G. F. H., a man, aged 32 at death, had epidemic encephalitis in December, 1924. He became very depressed and was admitted to the South Yorkshire Mental Hospital in July, 1926. He was then in an advanced Parkinsonian condition. There had been very little alteration in weight. In November, 1927, he was inoculated with malaria as a therapeutic measure. Rigors took place each day from November 21 till 27, when he collapsed and died.

The pituitary.—The pars anterior was congested and there was total destruction of the cytoplasm of many of the cells and dissociation of practically all (fig. 5.) The destructive changes were greater in this than in any other in the series except No. 3.

The nervous system.—The brain weighed 50 oz.

Mid-brain.—The cells of the substantia nigra were almost completely destroyed.

In the hypothalamic region there were considerable destructive changes, but a detailed account of the different nuclei is not given as the high temperature due to malaria could be regarded as a sufficient cause for changes in nerve-cells.

Case 9.

A. H., a woman, aged 34 at death, had an attack of "influenza" in February, 1924. She became very depressed and obsessed with different ailments which were regarded at the time as imaginary. She attempted suicide and was

admitted to the South Yorkshire Mental Hospital in May, 1924. There were then no neurological signs. In March, 1925, she was found to have phthisis. Early in April, 1928, Parkinsonism, which was considered to be post-encephalitic, was apparent. She also developed a left hemiplegia, the leg being more affected than the arm. The specific gravity of the urine was 1016 and albumin was present. She died in January, 1929, from tuberculosis and chronic epidemic encephalitis.

The pituitary.—The pituitary weighed 0·9 grm. and was heavier than any other in the series. There was a considerable amount of destruction of the cytoplasm of the cells of the pars anterior, and a fair amount of colloid between the two lobes.

The nervous system.—The brain weighed 44 oz. It was very pale and there seemed to be slight wasting, particularly on the right side. In Weigert-Pal preparations there was some degeneration of one pyramidal tract.

Mid-brain.—There was destruction of nerve-cells with separation of pigment in the substantia nigra.

Hypothalamic region.—There were destructive changes in the different collections of nerve-cells.

Case 10.

A. E. S., a woman, aged 62 at death, had epidemic encephalitis in March, 1924. She was admitted to the South Yorkshire Mental Hospital in October, 1926, and was then very depressed and complained constantly of inability to sleep. She was very Parkinsonian. She did not improve, but did not lose weight. There was no abnormality in the urine. She had an attack of influenza in March, 1929, and died from this after a short illness.

The pituitary.—This weighed 0·85 grm., a greater weight than any in the series except No. 8. There was great congestion in the anterior lobe. A fair proportion of eosinophiles was present, many of which were vacuolated. Nearly all the cells were unusually discrete; in some the cytoplasm was destroyed. In the posterior lobe the most noteworthy feature was some hyperplasia of the pars intermedia. Possibly there had been originally hyperplasia of the anterior lobe and later slight destructive changes.

The nervous system.—The brain weighed 43 oz. The right lateral ventricle was slightly larger than the left.

The nerve-cells throughout the whole nervous system were damaged, but most severely in the hypothalamic region and mid-brain.

The mid-brain.—There were severe destructive changes in the substantia nigra.

The hypothalamic region.—Status spongiosus was present. In the meninges of the hypothalamic region there was a collection of small round cells which extended into the brain substance (fig. 8); this may have been a terminal infection.

SUMMARY OF APPEARANCES IN PITUITARY AND HYPOTHALAMIC REGION AND OF SOME CLINICAL SYMPTOMS.

Case and duration of disease	Remarks	Pituitary			General remarks on nervous system	Hypothalamic region	Substantia nigra (and a note on Parkinsonism)
		Pars anterior	Pars intermedia	Pars nervosa			
I. — W. L., 2 yrs. 4 mths.	Diabetes insipidus. Obesity. Epilepsy	Hyperplasia in some areas	Hyperplasia. Increased connective tissue bounding islands of cells. Large amount of colloid in vesicles and cysts	More colloid and hyaline masses than usually seen Moderate amount of pigment	No wasting of brain	Less destructive changes than any in series. All nuclei affected, but no comparison possible	Slight changes. (Never more than a slight suspicion of Parkinsonism)
II.—G. E. R., 3 yrs. 8 mths.	Cachexia. Originally narcoleptic attacks. Later insomnia	Slight vacuolation of some cells. Decrease in size of pituitary	No conspicuous abnormality	Pigment ..	Some wasting, especially in hypothalamic region. The third and one lateral ventricle dilated	Severe destructive changes, probbably the most marked in the ventral nucleus	Severe changes. (Advanced Parkinsonism)
III. — M. M., 2 yrs. 6 mths.	Cachexia. Extreme drowsiness for many months	Very abnormal. Total destruction of cytoplasm of most cells. Two hæmorrhages	No conspicuous abnormality	Pigment ..	Wasting in hypothalamic region and in right postcentral area. The Sylvian aqueduct and third ventricle slightly dilated. Multiple hæmorrhages in brain-stem and hypothalamic region	Status spongiosus. All nuclei affected. Multiple hæmorrhages a characteristic feature	Severe changes. (Very advanced Parkinsonism)
IV. — D. F. B., 4 yrs.	No noticeable alteration in weight. Epilepsy	Not particularly abnormal	No conspicuous abnormality	No conspicuous abnormality	No wasting of brain. Multiple hæmorrhages in hypothalamic region and midbrain	Changes in nerve-cells, but less than in other cases, except I and VII. Multiple hæmorrhages a very characteristic feature	Changes comparatively slight. No difference in cells of two sides. (Rigidity mainly on one side)

V. — W. B., more than 2 yrs.	Cachexia. Drowsiness many months after onset of disease	Hyperplasia ..	Slight hyperplasia	No conspicuous abnormality	Brain weight rather low	Not available for examination	Severe changes (Advanced Parkinsonism)
VI. — A. N., 3 yrs. 11 mths	No noticeable alteration in weight. Insomnia	Slight hyperplasia	Slight increase of connective tissue at the junction of the intermedia and nervosa	No conspicuous abnormality	Brain unusually small	Severe destructive changes	Severe changes. (Advanced Parkinsonism)
VII.—G. F. G., 2 yrs. 2 mths.	Obesity. Epileptic before the onset of encephalitis	Cells unusually discrete	Large mass of colloid between the two lobes	Group of cells similar to mucous acini at junction of pars intermedia and nervosa	No wasting of brain	Less destructive changes than in the others, except I and IV. Corpus mamillare more abnormal than that of Case I	Very severe changes. (Very advanced Parkinsonism)
VIII.—G. F. H., 2 yrs. 6 mths.	Treated by malaria. No alteration in weight	Very abnormal. Dissociation of cells	No conspicuous abnormality	No conspicuous abnormality	No wasting of brain	Severe destructive changes	Severe changes. (Parkinsonism)
IX. — A. H., 5 yrs.	Cachexia, but patient had phthisis 4 yrs.	Abnormal. Destruction of cytoplasm	No conspicuous abnormality	No conspicuous abnormality	Slight wasting on right side of brain	Severe destructive changes	Severe changes. (Very advanced Parkinsonism)
X. — A. E. S., 5 yrs.	Weight well maintained. Insomnia	Originally hyperplasia followed by slight destructive changes	Hyperplasia ..	No conspicuous abnormality	Brain weight low. Right lateral ventricle slightly larger than left	Status spongiosus. Infiltration of meninges with small round cells	Severe changes. (Advanced Parkinsonism)

Discussion of the Appearances in the Pituitary.

It will be seen that in chronic epidemic encephalitis, although the pars anterior is sometimes normal, it may be either hyperplastic or atrophic, and the pars intermedia may also be hyperplastic. We may suppose that whereas the pituitary may react by hyperplasia, the virus of epidemic encephalitis ultimately produces secondary atrophic changes.

It is necessary to consider in the five cases that died from causes other than epidemic encephalitis how far the pathological changes may be ascribed to other diseases. Of the two patients with erysipelas, in one the pituitary was not very abnormal and in the other the disease was probably of too short duration to have had any influence.

Case 8 died from malaria, and the pars anterior is in many respects more abnormal than any of the others except that in Case 3, and in all probability this was due to malarial infection. We have not found any description in the literature of the pituitary in malaria, but there is a scarcity of information in general about the effect of different diseases on the pituitary.

Case 9 died from tuberculosis and the pituitary was heavier than any in the series, a feature common in this disease. No stress can therefore be laid on the appearances seen in the pituitary.

Discussion of Possible Relationship to Symptoms of Changes in the Pituitary and Hypothalamic Region.

Diabetes insipidus.—The relation of lesions in the pituitary to diabetes insipidus has been already discussed by one of us (see p. 47). The important fact which emerges from a comparative study of the hypothalamic region in the ten cases is that diabetes insipidus does not occur when the changes in this area are very severe, although it may do so when they are less intense.

Obesity.—That there is an anti-diuretic hormone produced by the pituitary, a deficiency of which causes diabetes insipidus, seems to us to be proved. There is as yet no equally good evidence of the importance of a pituitary hormone in relationship to obesity. The supporters of the possible hypophyseal origin of obesity regard the condition as due to a deficiency of hormone, but there is a difference of opinion as to which lobe of the pituitary is affected. If the posterior lobe is responsible, it is difficult to understand why obesity is not more commonly associated with diabetes insipidus. It may, however, be pointed out that in both the cases with obesity there was an unusual

increase of colloid in the posterior lobe, which may be regarded as a possible stasis of secretion. Otherwise, we find it difficult to express an opinion. In neither case was the anterior lobe particularly abnormal.

In all the ten cases of encephalitis there were alterations in the hypothalamic region. The changes were rather less advanced in the cases in which obesity existed. This corresponds with clinical observations that post-encephalitic obesity—where it occurs—is usually an early sequel. A. J. Hall and A. G. Yates [10] refer to the rapid increase in weight in some of their cases a few months after the primary attack of encephalitis, and state that this occurs before the recognized onset of Parkinsonism. According to Stern [16] also, obesity is usually an early symptom, but instances have been recorded of the appearance of obesity as long as four years after the acute stage. In Case 1 in this paper obesity was first noticeable about eighteen months after the acute attack, and polyuria appeared about the same time. In Case 7 a definite increase in weight took place about a year after the acute attack, and a severe degree of Parkinsonism was then present. Post-encephalitic obesity may be transient and followed by cachexia. On the other hand, it may persist until the death of the patient from the disease, or it may disappear with recovery of the patient from encephalitis. Whatever the mechanism of production of obesity, the exciting cause seems to be a mild rather than a severe lesion. Isolated examples of obesity and very severe destructive lesions in the hypothalamic region do not disprove this, as obviously this condition, unlike diabetes insipidus, when once produced, cannot disappear instantaneously.

Cachexia.—The relationship of destructive changes in the pars anterior to the presence of cachexia in epidemic encephalitis is doubtful as it is obviously debatable as to which is cause and which is effect. In Case 3 the patient was very emaciated, and destructive changes in the pars anterior were at a maximum. However, Case 5 lost weight considerably, and the pars anterior was hyperplastic. It therefore seems the more probable that cachexia in epidemic encephalitis is independent of any changes in the pituitary.

In the nine cases where the hypothalamic region was examined, severe pathological changes were found in this area in seven, although cachexia occurred in two only of them. We therefore hesitate to conclude that such changes are the cause of the condition, although it must be admitted that some time must elapse for cachexia to be established if destructive changes in the nervous system are a cause.

There is a type of Parkinsonism accompanied by severe wasting.

That there is necessarily a common cause for the two conditions seems, however, to be disproved by such a case as No. 7 in our series. This patient began to gain in weight after severe Parkinsonism was established; the destructive changes in the substantia nigra were severe, those in the hypothalamic region comparatively slight.

Disorders of sleep.—The pathology of disturbances of sleep is uncertain, although it has been much discussed. Various theories about the nature of sleep are discussed, and there is reference to much of the literature in papers by Adie [1], Fulton and Bailey [6] and Kinnier Wilson [19]. The latter author remarks on the incomplete nature of pathological knowledge on the subject of sleep disorders. It has been suggested that the pathological drowsiness of epidemic encephalitis may be of pituitary origin. However, Cases 5 and 6 suffered from sleep disturbances and the pituitary in both instances was very slightly abnormal, so it seems improbable that abnormalities in the pituitary in the other cases played a part in the causation of these symptoms.

In a disease such as epidemic encephalitis which attacks the nervous system diffusely the problem is obviously a difficult one. As is well known, the disturbances of sleep are of four kinds: (*a*) hypersomnia; (*b*) insomnia; (*c*) reversal of the sleep rhythm, and (*d*) narcolepsy, and which type predominates may vary in the same patient at different stages of the malady. Case 2, for instance, at an early stage had narcoleptic attacks and later complained of insomnia. Case 3 originally suffered from insomnia, and two years later from hypersomnia.

Hypersomnia, or excessive sleepiness, is found as a symptom in several conditions, cerebral tumours being perhaps the commonest apart from epidemic encephalitis. Statements vary as to the frequency of its occurrence in tumours in different parts of the brain, but it is probably most common in tumours in the neighbourhood of the hypothalamus and pituitary.

It will be seen that the hypothalamic region was affected in all the ten cases of the series, but it does not, of course, necessarily follow that it was responsible for all the sleep disturbances. Cases 2 and 6, for example, frequently complained of spontaneous pains in the limbs, and this might be sufficient to account for insomnia. The existence of old hæmorrhages in the hypothalamic region in Case 3 is interesting in view of the onset of extreme drowsiness about ten months before death.

A point of great importance which has been little considered is the frequency of changes in the hypothalamic region without disturbance of

sleep. Stief [17] described various changes in the hypothalamic region in general paralysis and in arterio-sclerotic disease. Yet there is no mention of these patients having had disorders of sleep. An examination of the photomicrographs in Stief's paper inclined us to the opinion that the cell destruction was small and the increase of neuroglia very great as compared with these cases of chronic epidemic encephalitis. We have, however, felt it advisable to examine the hypothalamic region from cases in which there was extensive degeneration of the nervous system in order to make a more certain comparison. We selected brains from cases of Huntington's chorea and general paralysis of the insane for this purpose. In the hypothalamic region from the case of Huntington's chorea the different collections of nuclei could easily be identified and there was very little destruction of nerve-cells. The same was true in the hypothalamic region from a case of general paralysis of the insane with the difference that there was considerable increase of neuroglial nuclei.

There is another point of view that seems worth mentioning. Perhaps there is a not unnatural tendency to overstress the histological appearances without considering biochemical differences that may exist in different conditions, but, indeed, little work has been done in this direction.

One of us has found by chemical analysis of the nervous system that a raised calcium content is relatively common in epidemic encephalitis, but is rarely found in general paralysis of the insane. Why one nervous disease should be accompanied by increased calcium, and why this should not be so in a severe degenerative condition such as general paralysis of the insane, seems rather mysterious, but in view of Demole's work it may have some bearing on disorders of sleep. Demole's experiments resulted from the observations of Cloetta and Thomann that the amount of calcium in the blood falls during sleep, a possibility being that it is concentrated in the brain. Demole [4] found that by injecting weak solutions of calcium salts into the region of the floor of the third ventricle, sleep could be induced in animals, and that an antagonistic effect was produced by potassium salts. The specific action of these salts was confined to the hypothalamic region.

These striking experiments have been repeated by Marinesco, Sager and Kreindler [14], who confirmed the observation that calcium injections into the hypothalamic region favoured sleep. These workers were also able to produce reversible sleep phenomena in animals.

SUMMARY.

(1) In chronic epidemic encephalitis there is frequently some change in the pituitary.

(2) The hypothalamic region of the brain in chronic epidemic encephalitis is more severely affected than any other area except the substantia nigra of the mid-brain. The changes in the two regions are usually, but not invariably, parallel.

(3) In all the cases of epidemic encephalitis the changes in the hypothalamic region were greater than in the same area in brains from cases of Huntington's chorea and general paralysis of the insane, where elsewhere there were severe degenerative changes.

(4) Severe lesions in the hypothalamic region do not give rise to diabetes insipidus nor to obesity, but less intense lesions may cause these conditions.

The part played by the pituitary in the production of obesity remains uncertain.

(5) Cachexia is probably independent of any changes in the pituitary. There is no absolute proof, although there is a possibility, that pathological alterations in the hypothalamic region are the cause of cachexia. On the other hand, it seems certain there is no causal relationship between destruction of the substantia nigra and cachexia.

(6) There is not any definite relationship between disturbances of sleep in epidemic encephalitis and alterations in the anterior lobe of the hypophysis. As the hypothalamus was affected in all the brains, and is not commonly the chief site of attack in other degenerative diseases, disturbance of its function—perhaps due to increase of calcium salts—probably plays some share in the causation of disorders of sleep. An increase of calcium salts does not usually occur in conditions such as Huntington's chorea and general paralysis of the insane.

(7) Hæmorrhages were more common in the hypothalamic region and mid-brain than elsewhere, and may have been the cause of sudden death in one young patient.

The writers are very much indebted to Professor Hall for some helpful criticism and advice. They wish to thank the Medical Superintendent and the Senior Medical Officers of the South Yorkshire Mental Hospital for facilities for studying the cases on which this paper is based; Dr. Thorpe, the pathologist, for the supply of material; and Dr. Elizabeth Sykes for information about the weights of patients.

PLATE VIII.

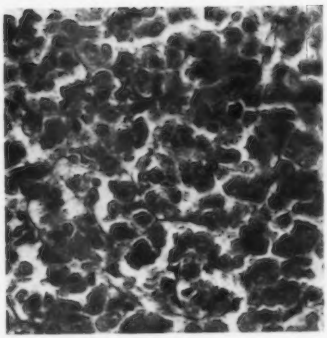

FIG. 2.

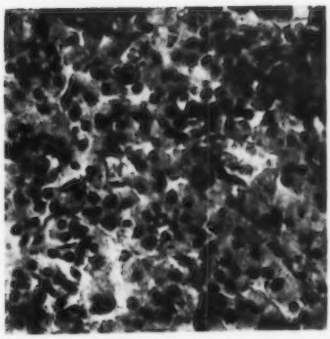

FIG. 3.

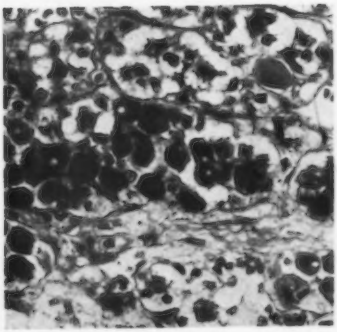

FIG. 4.

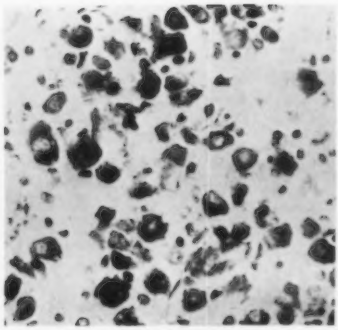

FIG. 5.

To illustrate article by Elizabeth Cowper Eaves and Margaret M. Croll.

PLATE IX.

FIG. 6.

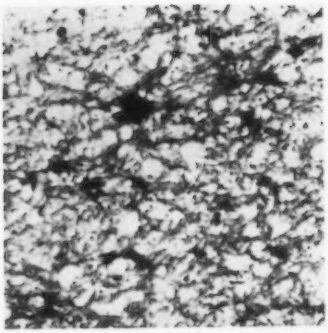

FIG. 7.

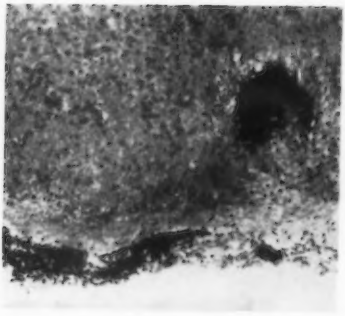

FIG. 8.

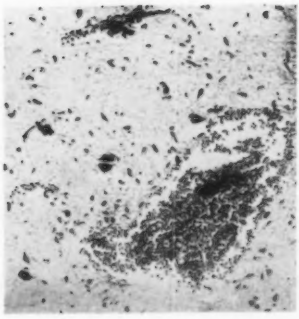

FIG. 9.

To illustrate article by Elizabeth Cowper Eaves and Margaret M. Croll.

The expenses of the research were defrayed by a grant from the Medical Research Council.

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DESCRIPTION OF ILLUSTRATIONS, PLATES VIII AND IX.

Fig. 2.—Pars Anterior of the Pituitary. Originally × 500 reduced to $\frac{2}{3}$. Normal for comparison with fig. 3.

Fig. 3.—Pars Anterior of the Pituitary. Originally × 500, reduced to $\frac{2}{3}$. *Case* 5. Hyperplasia. The nuclei are more numerous and more darkly staining than those in the normal pars anterior in fig. 2. Some of the cells are binucleated.

Fig. 4.—Pars Anterior of the Pituitary. Originally × 500, reduced to $\frac{2}{3}$. *Case* 3. Atrophy. Many of the cells have lost all the cytoplasm. About the centre of the field is a group of swollen eosinophiles.

Fig. 5.—Pars Anterior of the Pituitary. Originally × 500 reduced to $\frac{2}{3}$. *Case* 8 (treated with malaria). Dissociation of cells which are practically all isolated and vacuolated.

Fig. 6.—Hypothalamic region. Originally × 40, reduced to $\frac{2}{3}$. *Case* 3. Hæmorrhages—most of them not recent.

Fig. 7.—Hypothalamic region. Originally × 500, reduced to $\frac{2}{3}$. *Case* 3. Status spongiosus.

Fig. 8.—Hypothalamic region. Originally × 140, reduced to $\frac{2}{3}$. *Case* 4. Hæmorrhage.

Fig. 9.—Hypothalamic region. Originally × 140, reduced to $\frac{2}{3}$. *Case* 10. Numerous round cells in the meninges, extending into the substance of the hypothalamic region.

EXPERIMENTAL DIABETES INSIPIDUS.

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THAT there is a close relationship between water exchange and the function of nervous tissue of the brain-stem surrounding the sella turcica has been indicated by a number of different observations, clinical and experimental. Tumours of this region are sometimes associated with either temporary or permanent polydipsia and polyuria or diabetes insipidus. Experimental lesions of this region, even very minute injuries, have been followed by increased water-intake and urine-output which lasted only a few hours or days, but in a few instances seemed to be permanent. Camus and Roussy (1922), and Bailey and Bremer (1921) in their experiments, each had one animal in which the diabetes insipidus seemed to be permanent. The production of permanent effects, however, is still entirely a matter of chance. Experimentally the problem is still incompletely solved. We do not know what structures are injured when the diabetes is produced, nor do we know how the lesion operates.

For the solution of this problem it is important to be able to produce a permanent effect consistently and under controlled conditions. The rat is a suitable animal for this purpose. It will be shown below that permanent polydipsia and polyuria may be produced in this animal very simply by means of brain-stem puncture, while the brain is large enough to permit definite localization of the injury to be made. In addition, the size of the rat allows it to be kept in a cage in which the water-intake, urine-output, and other changes can be accurately measured.

In the present paper the method of making the puncture is described, and records of the effects on water-intake and urine-output produced in this way are given. The results of the histological study of the brains of these animals will be described in a later paper.

METHODS.

The method of puncturing the brain (fig. 1) is the same as that used by Philip Smith (1927) in his operations on the pituitary body. The anæsthetized rat is tied on its back to a small board and the hair is

clipped away from the skin of the neck. A longitudinal incision about 1 cm. in length is then made to the right of the midline to expose the masseter muscle, as shown in the drawing in fig. 1. A blunt probe is inserted at the point indicated and pushed straight downwards until it

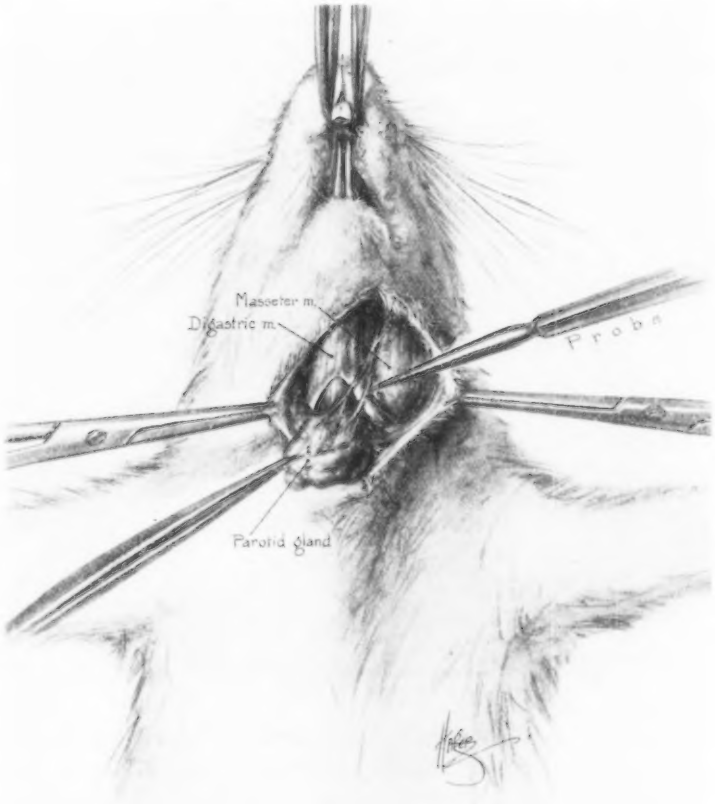

FIG. 1.—Drawing showing incision in rat's neck and opening between the masseter and diagastric muscles through which the base of the skull is exposed.

reaches the auditory bulla which can be easily recognized by its spherical shape. A second probe is introduced beside the first and the two are spread apart in the longitudinal direction. In this way the muscles covering the auditory bulla may be separated without injuring the muscles themselves or the surrounding blood-vessels. The area of bone

enclosed by the dotted line in fig. 2 is stripped of adherent membranes and other tissues so that the median suture may be located. Then a stab is made directly through the bone with the scalpel shown in fig 2. The depth of the thrust is regulated by means of a drop of solder attached at the side of the scalpel to act as a stop. The bone is soft enough even in old animals to permit easy penetration of the scalpel. A sagittal view is shown in fig. 3.

Since the albino rat is strongly resistant to infection no antiseptic

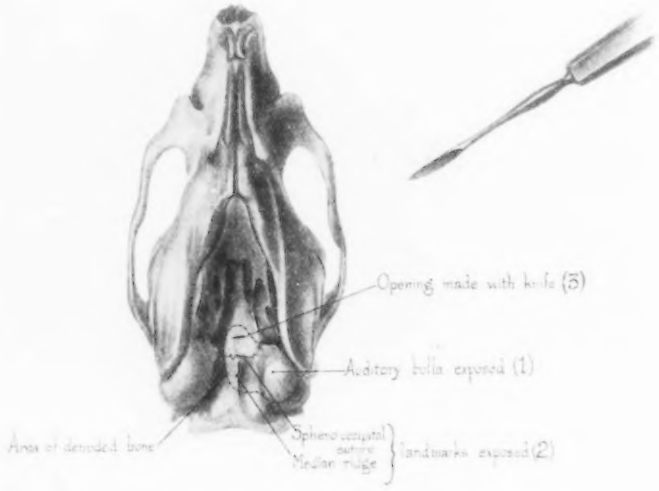

FIG. 2.—Drawing of the skull of the rat and the scalpel used in making brain-stem punctures.

precautions are necessary for the operation. None of the thirty-six animals used in the present experiment became infected.

The rats were kept separately in cages described in detail elsewhere (Richter and Wang, 1926) (Richter, 1927) in connection with studies on running activity. These cages consist of a small living compartment with easy access to a revolving drum in which the animal may run. The revolutions of the drum are recorded on a ratchet cyclometer. The cage contains, besides a space large enough for an adult rat to sleep in, a food-box and a graduated inverted watering-tube. Daily records were made of running activity and food and water-intake. The urine was collected from both the living compartment and the revolving drum by

means of pans with funnel-shaped bottoms placed beneath the mesh-wire floor of the cages and leading into small graduated cylinders. The condition of the reproductive tract was studied by means of daily vaginal smears. And finally, the rate of growth was charted by weekly records of the body-weight.

Thirty-six female rats were used for the experiments, their ages at the time of the brain punctures varying from forty to one hundred and twenty days. Females were used exclusively because, by means of vaginal smears, changes in the function of the sex-glands can be most

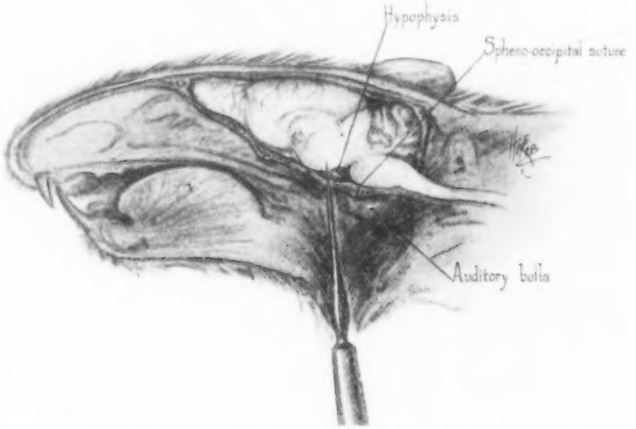

FIG. 3.—Sagittal section of the rat's head showing where the scalpel pierces the skull and brain.

easily detected, and such changes are significant because they can be produced by injuries to the pituitary glands.

RESULTS.

The brain-stem was punctured at different levels within a very limited region. This region can be located in the skull in fig. 2 with relation to the spheno-occipital suture. In the average adult rat it extends from 3 mm. above the suture to 0·5 mm. below. This part of the skull covers the pituitary gland and leaves a margin of approximately 0·5 mm. above and below.

Of the thirty-six animals used for these experiments seven showed

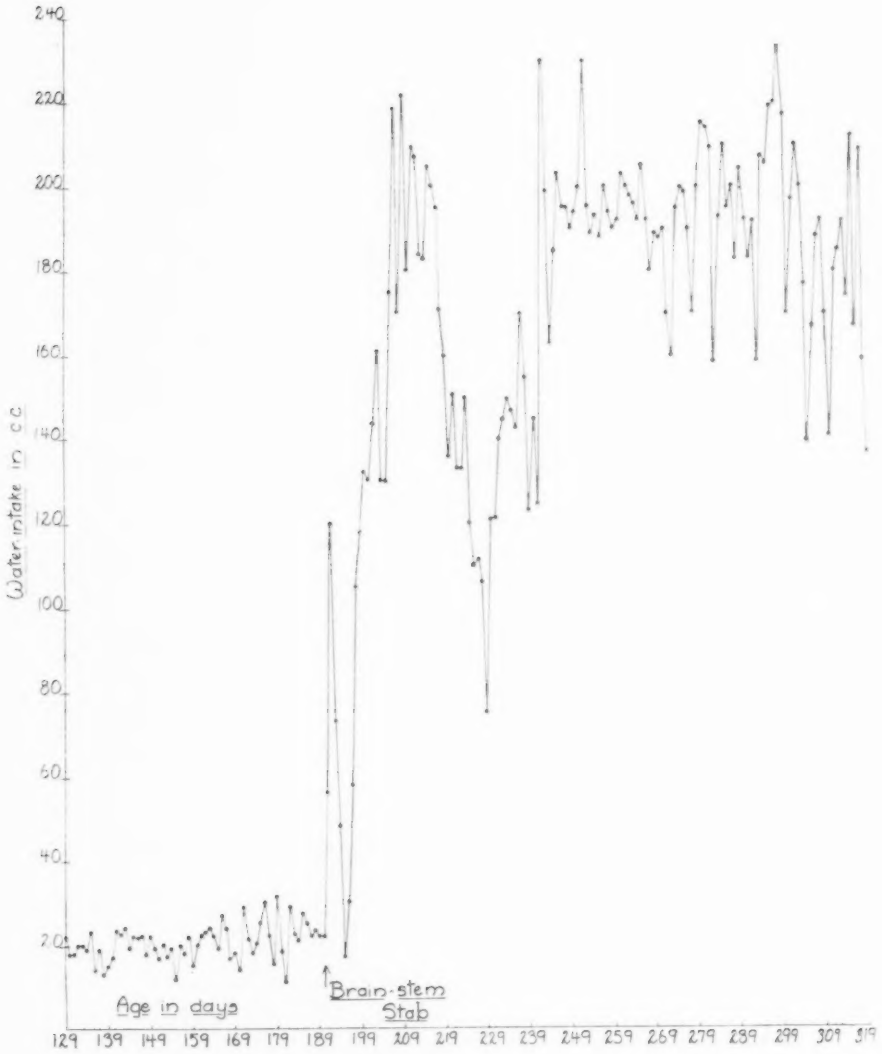

FIG. 4.—Water-intake record showing effect of brain-stem puncture. The ordinates give water-intake in cubic centimetres and the abscissæ the duration of the experiment in days. Rat 430.

an increase in water-intake as a result of the puncture. Post-mortem examination showed that the scalpel penetrated the skull in all seven at the same level, 2·5 to 3 mm. anterior to the spheno-occipital suture, a level which corresponds to a point near the anterior margin of the pituitary gland. In the twenty-nine rats which showed no increase in water-intake the scar on the skull was located below or above this level. Subsequent experiments have demonstrated beyond question that a puncture at this place produces the diabetic condition with a fair degree of certainty, but an absolutely accurate location of the significant point in the skull must wait until the vulnerable structure in the brain-stem has been definitely established by histological methods. And for the same reason, of course, the necessary depth of penetration cannot yet be discussed.

These experiments do not exclude the possibility that the results of the puncture may be caused indirectly through rupture of blood-vessels, or other interference with the circulation of the vulnerable area, rather than through the interruption of nervous pathways or the destruction of special nuclei.

As has been stated above, the increase in the water-intake produced by these brain-stem punctures is always permanent. It may or may not be very great, however, and there is considerable variation in the interval between the onset of the post-operative effect and the time when the maximum is reached. Because of these individual differences three curves will be presented.

The record in fig. 4 was obtained from the animal which showed the largest increase in water-intake. The water-intake in cubic centimetres is indicated on the ordinates and the age of the animal in days on the abscissæ. Before the brain-stem was punctured the average daily water-intake was approximately to 20 c.cm., and within the first two days after the operation it increased to 120 c.cm. On the fourth day it returned to the normal level, where it remained for that day only. A precipitous increase began on the fifth day, so that after two more days a level of over 200 c.cm. per day was reached. With the exception of a short interval of diminished intake occurring thirty-five days after the operation, this high level was maintained until the animal was killed six months later.

In another rat the increase in water-intake was not as great as in the previous record, but after the maximum level was reached it was maintained constantly to the end of the experiment. In this animal the puncture was not made with the scalpel, but with a thin probe to which

a small steel loop was attached. A longitudinal opening was made in the skull with a scalpel before this instrument with the loop was inserted. It was whirled around once or twice before it was removed. The idea was to make a small circumscribed spherical lesion.

In the next record, fig. 5, the amount of 104 c.cm. was reached on the day following the operation. Thereafter for ninety days a gradual decrease occurred until a permanent level of 55 c.cm. was reached.

The water-intake of another animal increased steadily for seventy

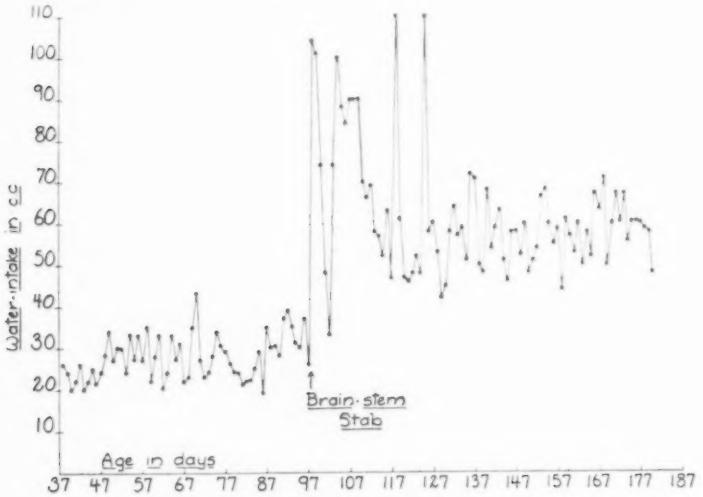

FIG. 5.—Record showing effect of brain-stem puncture. Rat 471.

days after the puncture to 75 c.cm. daily and remained at this level fairly constantly until the animal was killed sixty days later.

In the animal the record of which is shown in fig. 6 no definite effect was noticeable for fifty days, except for a slight rise on the day following the operation. Then the water-intake increased steadily from day to day for sixty days, until a permanent daily level near 48 c.cm. was reached.

These graded differences in the effect of the puncture will undoubtedly be of value in the localization of the part of the brain responsible for the increase in water-intake. It is to be expected that in the rat of fig. 3 the puncture must have been made exactly in this area, for it is difficult to conceive of the production of a greater increase. In the other rats

the puncture must have struck the area but not so fully as in the afore-mentioned rat.

The urine output of these animals was similarly increased. In the animal which showed the largest increase in water-intake (see fig. 3)

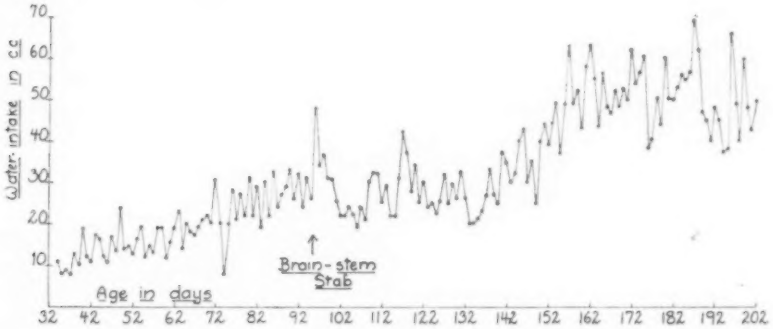

FIG. 6.—Further records showing effects of brain-stem punctures on water-intake. Rat 436.

the urine-output averaged about 10 c.cm. each day less than the water-intake, although the output was occasionally greater than the intake. The other animals showed approximately the same difference between water-intake and urine-output.

While taking the records on urine-output, we were able to obtain information which may throw some light on the sequence in which the

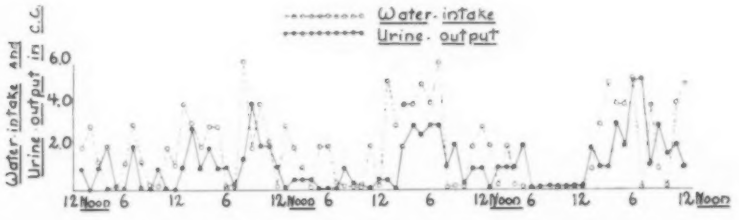

FIG. 7.—Chart of the hourly water-intake and urine-output for four successive days. Rat 430.

polydipsia and polyuria produced by the brain-stem puncture appear. Diurnal rhythms are known definitely to occur each day in both water-intake and urine-output. With this fact as a basis we believed that hourly records of the water-intake and urine-output might reveal which precedes the other. In this way it was established that usually the peak

of the water-intake precedes the peak of the urine-output by one or two hours. A record of this kind from one of the diabetic rats is presented in fig. 7. It shows the water-intake and urine-output for four successive days, with the daily rise in both functions occurring between 12 midnight and 8 a.m., and the peak in water-intake preceding that of urine-output.

The other functions of the body were not consistently altered by puncture of the brain-stem. It seemed likely that there might be an increase in food-intake in the rats since occasionally a ravenous hunger is present in human diabetics in addition to the great thirst. However, the food-intake showed no change at all in any of the animals.

The body-weight showed no constant change. In two of the animals it decreased slightly, in one there was a slight increase and in the others no change at all.

Similarly the spontaneous running activity, as measured in the revolving drum, was not affected in any constant way. Animals which ran well before the puncture continued to do so afterwards, and those which were poor runners before remained inactive. The four- or five-day cycles of activity, characteristic of the female and associated with ovulation, were present in all of the seven animals at some time following the operation, but in four only were they as regular as they are in a normal rat. In the other three the activity showed marked irregular fluctuations.

Inasmuch as running activity is known to be closely associated with the function of the reproductive tract, being related to ovulation every fourth or fifth day, it was to be expected that when the running cycle occurred normal cyclical changes in the vaginal smear would be present also; and this was found to be the case. In the afore-mentioned three animals which showed additional long cyclical fluctuations of activity, however, the vaginal smears were markedly abnormal. During the interval when the activity was very low, the vaginal smears showed only the leucocytes and epithelial cells which are characteristic of the diœstrous condition of the reproductive tract. This picture of activity and vaginal smear is very similar to that found by Wang and Guttmacher (1927) in animals with injured ovaries. On the basis of this observation the conclusion may be drawn that in these three animals the pituitary gland was injured so that the function of the ovaries was disturbed and the running activity affected. In the other four animals it is very probable that there was no interference whatever with the normal functions of the pituitary gland.

It is of interest to note that in the animal with the largest increase in water-intake there was a marked loss of hair on the fore and hind legs and over part of the back, so that at the time this animal was killed the skin was entirely bare over these areas.

Summary.

(1) It was shown that in the rat a marked and permanent increase in water-intake and urine-output may be produced by a fine puncture made in the brain-stem near the pituitary gland.

(2) The exact place was located in the skull through which a puncture with a scalpel regularly produces a polydipsia and polyuria.

(3) Although the effect is permanent, the curve of the increase varies considerably. The maximum increase may be reached on the first day after the puncture, or the increase may be very gradual, so that the maximum is not reached for several months afterwards.

(4) The increase in water-intake may be very great. One animal drank almost twice its body-weight each day.

(5) The effects produced by these brain-stem punctures are limited to the increase in water-intake and urine-output. There is no increase in food-intake, and body-weight remains unaffected. There are no constant changes in the spontaneous running activity or in the sexual cycles. One animal showed marked loss of hair on the inside of its legs.

(6) The absence of changes in the sex cycle suggests that the pituitary gland was not injured in these operations.

(7) Evidence is presented which indicates that polydipsia precedes polyuria.

(8) The nature and the localization of the lesion in the brain-stem will be described in a later paper.

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TUMOUR OF THE GASSERIAN GANGLION: SHEATH NEUROMA.[1]

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TUMOURS of the Gasserian ganglion of any type are uncommon, and most neoplasms that involve it arise from neighbouring structures and invade the ganglion secondarily. Only a small number of primary tumours have been placed on record, and on this account the following case seems worthy of description.

REPORT OF CASE.

Clinical features.—A woman, aged 28, came to the Mayo Clinic, May 20, 1929, complaining of anæsthesia and paralysis affecting the left side of the face. In 1924, for a period of three months, she had had sharp "jabbing" pains in the region of the left ear. A year later these pains had returned to the left ear and its vicinity for a period of six weeks, after which the pain had been replaced by a dull ache around the left eye, which had continued, with varying intensity, for two years. Two years before admission she had noticed that when she rubbed her lower lip a quiver, like an electric current, would begin in the left ear; this had been accompanied by pain in the same region, at times very severe for a few seconds. Two and a half years previously the muscles of the forehead had become paralysed, and at the same time she had had some discomfort, associated with crackling noises, in the left temporo-mandibular joint. Gradually anæsthesia had developed, until about one and a half years before admission there had been left-sided anæsthesia which had affected the forehead and anterior part of the scalp, the eye, the cheek, the nose, both upper and lower lips, the lower jaw, the tongue and the roof of the mouth. Preceding each advance of the anæsthesia there had been severe transitory pain in the area to be affected. During the same period paralysis of the left side of the face developed. For the last year, also, the patient had had a sensation as of stopping up of the Eustachian tube, and for the last six months an impression of obstruction in the left side of the nose. In the last ten months she had had thirty corneal ulcers in the left eye. Eighteen

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months before admission she had been very drowsy for a few months; she said she could sleep anywhere, at any time.

Examination disclosed complete paralysis of the peripheral type of the left fifth and seventh nerves, except that a little power remained in the platysma, no doubt due to the presence of anastomoses between the second and third cervical nerves and the inframandibular branch of the facial nerve. Auditory acuity was normal on both sides. There was loss of taste on the anterior part of the left side of the tongue. The corneal reflex was absent on the left side. The movements of the left half of the soft palate were perhaps a trifle less free than of those of the right half, but there was no difference between the palatal reflexes, and no paralysis of the pharyngeal muscles. The fundi and visual fields were normal.

The association of pain and, later, anæsthesia in the territory of the fifth nerve suggested that a destructive process, probably neoplastic, was active in the cave of Meckel: and the paralysis of the seventh nerve, which included the fibres derived from the nervus intermedius, made it likely that the process had transgressed the middle fossa of the skull and was active in the posterior fossa. On the other hand, if the tumour were pressing on the seventh nerve and the nervus intermedius in the posterior fossa, it was extremely difficult to explain the escape of the fibres of the left eighth nerve, which were repeatedly shown to be intact. We considered the possibility of extracranial extension of the tumour through the foramen ovale, but we were unable to demonstrate this clinically; nor was there any radiographic evidence of destruction of bone in this region. A third route by which such a process might have reached the facial nerve was by erosion of the petrous part of the temporal bone until it involved the Fallopian canal; but of this there was no radiographic evidence. We concluded that the tumour, growing down from the cave of Meckel toward the upper part of the internal meatus of the ear, involved first the facial nerve and then the nervus intermedius, and that possibly, as is the case with conducting fibres generally, the efferent motor nerve was more sensitive to the pressure of the neoplasm than was the afferent sensory nerve. The feeling of stuffiness in the Eustachian tube could be explained by its infiltration by tumour cells, since the cartilaginous part of the tube is in close proximity to the foramen ovale. On the other hand, it might have been due to paralysis of the tensor tympani muscle, as a result of the destruction of the nerve fibres passing through the motor root of the fifth nerve to the otic ganglion.

Surgical features.—The surgical problem which presented itself was to decide which cranial fossa should be investigated first. As the pain had preceded the facial palsy, we decided to begin by exploring the middle fossa, as for section of the sensory root of the fifth nerve: if necessary, we intended to explore the posterior fossa at a subsequent date. The patient had returned home for a period, and exploration of the middle fossa was carried out, June 24, 1929. When the ganglion was exposed, its third and second divisions and the ganglion itself were seen to be of a dark maroon colour, and the dura

over the ganglion was much more adherent than normally. When the arachnoid over the sensory root was opened, the fibres of the root were at first indistinguishable, as they were surrounded by maroon-coloured gelatinous material. Portions of this material, and a certain amount of tissue from the posterior margin of the ganglion, were removed for histological examination. This procedure revealed that the ganglion had been pushed forward, so that instead of passing downward and forward to reach the foramen ovale, the third division of the fifth nerve passed downward and backward. There was no evidence of infiltration of the petrous portion of the temporal bone to explain the paralysis of the seventh nerve. As complete removal of the tumour was obviously out of the question, the operation was completed by passing a gauze drain down to the ganglion and closing the wound in layers. The latter procedure was somewhat difficult, as the temporal muscle was so atrophied and friable that its approximation was unusually tedious. The patient had a speedy convalescence; she sat up on the third day, and left the hospital on the fourth day for a neighbouring convent. It was decided not to perform the suboccipital decompression unless symptoms of increased intracranial pressure should appear at a later date.

When the patient was last heard from, October 11, 1929, she had resumed teaching, was in good health, and had not suffered any disability from the exploration.

Pathology.—The cells of the tumour were small, with a slight amount of agranular cytoplasm; the nuclei almost filled the cells. The majority of the nuclei were oval or irregular, and stained deeply with hæmatoxylin or thionin; a few still more deeply staining granules also were present. The nuclei did not contain nucleoli. The cells did not show processes when stained with Mallory's phosphotungstic acid hæmatoxylin. The cells of the tumour were arranged in columns and in tubules (Plate X, fig. 1). The peculiarly-formed tubules or alveoli were mainly composed of two concentric rings of cells, with the longer axes of the nuclei pointing toward the centre of the alveolus (fig. 2). This arrangement was present throughout, except in the solid columns of cells, in which the nuclei in the centre had no definite arrangement, although the peripheral nuclei were frequently arranged in palisade-like rows with their longer axes parallel to each other (fig. 3). Few mitotic figures were present, and few normal ganglion cells were found, but there were some degenerated cells and remnants of cells in which a little chromatin substance could be demonstrated with the toluidin blue stain. In some of the alveoli formed by the peculiarly arranged tumour cells, remnants of ganglion cells were seen, but normal cells were not so surrounded. Occasionally beginning proliferation of the endocapsular cells was noted, and in such regions there was beginning degeneration of the ganglion cells (fig. 4). The supporting structure was increased in amount, but not to an excessive degree, and in parts it had undergone hyalinization. Psammoma bodies were rare; only one was seen in all the sections studied, and contrary to the findings of most other observers of tumours of the Gasserian ganglion, plasma or other inflammatory cells were

not found. There were many bundles of nerve-fibres here and there, broken up by columns of tumour cells, and the axis cylinders of such bundles showed degeneration.

The cells composing the tumour simulated somewhat those normally seen in the arachnoid, and called arachnoid cell clusters. However, the latter are differently arranged and have more cytoplasmic processes: they form whorls, with a heavy supporting structure, and psammoma bodies are abundant. On the other hand, in this tumour neither whorls nor psammoma bodies were to be seen. The cells of the tumour strongly resembled those which occur in the capsule of the normal cell of the Gasserian ganglion. The possibility that such cells can produce a tumour was first recognized by Marchand.

In Marchand's case the cells of the tumour and their arrangement and relation to the ganglion cells were similar to those in the case described here. Marchand stated: "These cells are identical with the capsule cells of the ganglion cells." Similar cases have been described by others, under various names, such as alveolar sarcoma (Krepuska), or endothelioma (Sachs and Rand), but their possible origin from ganglionic capsular cells has not been discussed. Marchand reviewed the literature of tumours of the Gasserian ganglion, and found a few cases like his own which had been otherwise classified. Sachs reported a tumour which, from his description, was of the same nature as that reported in this paper; the tumour cells were arranged around "empty spaces in which ganglion cells had been lying, but no traces of the cell remained." He classified it as an endothelioma.

In a case described by Dercum, Keen and Spiller, Spiller observed that when the tumour (an endothelioma) invaded the Gasserian ganglion many nerve-cells were destroyed and there was proliferation of the capsular cells. Spiller considered this picture to be secondary to that of invasion of tumour and destruction of ganglion cells. Krepuska, earlier than Marchand, described a tumour which histologically was an alveolar sarcoma and was similar to that in the case described in this paper. More recently Rand reported a case which he stated was similar to that of Marchand, and in which he classified the growth as an endothelioma.

The origin of the ganglion capsular cells is uncertain, and on this account it is easy to understand the confusing terminology used in classifying tumours arising from them. Lenhossek said that these capsular cells "consist of connective tissue which passes into the sheath of Henle of the axis cylinder process."

Marchand considered the cells similar to the cells of the sheath of

Schwann, or indifferent endothelial cells. As pertaining to this the experiments of Harrison may be noted, in which he removed the ganglionic crest of *Amblystoma punctatum*. Motor nerves developed with axis cylinders, but without cells like those in the sheath of Schwann. Harrison said, "Sheath cells are not mesodermal, but arise for the most part from the ganglionic crest in connection with the spinal ganglia," and, "the sheath cells are to be regarded as the neuroglia of the peripheral nerves." However, Bartelmez and Evans stated: "In no form have they (neural crest cells) been followed with certainty from their origin to their differentiation into ganglion, sheath and capsular cells." Stout described a tumour of the ulnar nerve which, like most sheath neuromas of the Gasserian ganglion, had produced metastasis in the regional lymph nodes and had also formed some rosettes. Some "schwannomas" of the peripheral nerves are similar to the tumour described here.

Until a definite origin is assigned to the ganglionic capsular cells, it seems best to classify this tumour as a sheath neuroma, and although it has some similarity to the neurocytoma of the retina, it will possibly be ultimately classified with the gliomas.

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PLATE X.

FIG. 1.

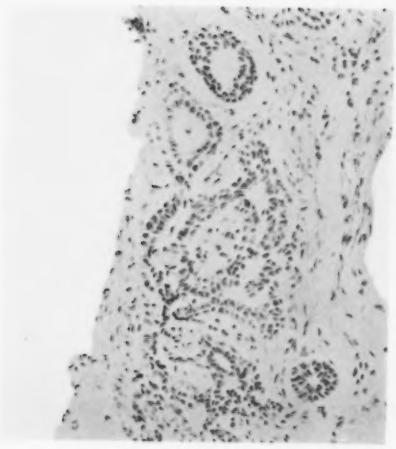

FIG. 2.

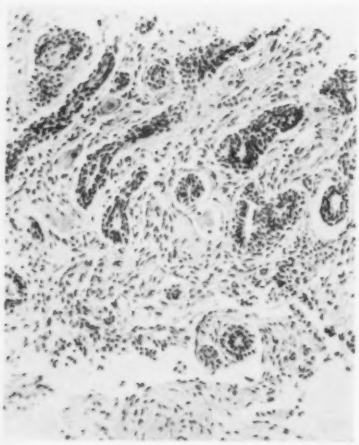

FIG. 3.

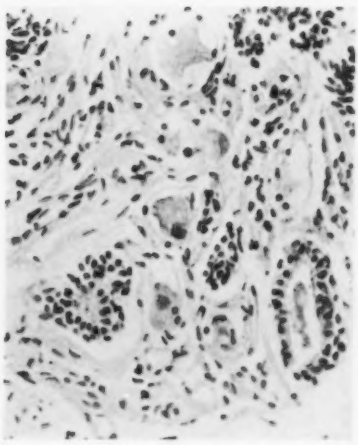

FIG. 4.

To illustrate paper by James R. Learmonth and James W. Kernohan.

[10] Stone, L. S. "Experiments on the Transplantation of the Placodes of the Cranial Ganglia in the Amphibian Embryo. IV. Heterotopic Transplantations of the Post-auditory Placodal Material upon the Head and Body of *Amblyostoma punctatum*," *Journ. Comp. Neurol.*, 1929, **48**, 311-330.

[11] Stout, A. P. "A Tumour of the Ulnar Nerve," *Proc. New York Path. Soc.*, 1917-19, **17-19**, 1-12.

Description of Illustrations, Plate X.

Fig. 1.—Section of tumour showing the arrangement of the tumour cells in tubules and columns. The comparatively acellular supporting structure is seen. (Thionin stain, × 150.)

Fig. 2.—A portion of fig. 1 showing the two rows of tumour cells forming the tubules or the columns; no mitotic figures are seen in this field. (Thionin stain, × 300.)

Fig. 3.—This area shows tumour masses similar to those in figs. 1 and 2, but with ganglion cells in the supporting structure; the lumina of the tubules are empty except for débris. (Hæmatoxylin and eosin stain, × 175.)

Fig. 4.—The ganglion and capsular cells are intermingled with the tumour cells; two ganglion cells show proliferation of the capsular cells; these cells show early signs of degeneration. (Hæmatoxylin and eosin, × 350.)

Notices of Recent Publications.

Lewandowsky's Handbuch der Neurologie. Ergänzungsband: 1ster Teil, 4ter Abschnitt. Die traumatischen Lasionen des Rückenmarkes auf Grund der Kriegserfahrungen. Von O. Foerster. 1929. S. 207. Berlin: Julius Springer. Price 39 Marks.

Previous volumes in this series have already been reviewed in this Journal and in the present Professor Foerster continues his detailed collection and analysis of war injuries of the nervous system.

The high opinion of this comprehensive work expressed in respect of previous volumes is equally deserved by the present section. In this the author gives a detailed account and analysis of a large series of personally observed cases of war injury of the spinal cord, and has collected all similar cases reported in neurological literature since 1914. The enormous mass of information thus assembled does not make easy reading, and the great value of the book will be as a comprehensive and accurate work of reference.

The author does not deal primarily with the symptomatology of war injuries of the cord, but is concerned with the various ways in which gunshot wounds, stab wounds, explosions, electric shocks and the numerous forms of bodily injury may produce lesions of the spinal cord. Thus direct injury to the cord, injuries of the vertebral column, of the limb girdles, falls and blows on the back are all considered in relation to the types of spinal cord lesion that may be associated with them. In the second section of the book, the minute anatomy of these cord lesions, recent and late, and the secondary processes resulting from them are described in detail.

The author has produced a complete record of the various kinds of bodily injury which may result in spinal cord lesions, and of the pathological anatomy of such lesions.

Les Acrocyanoses. Par F. Lavani. Paris: Masson et Cie. 1929. Pp. 280. Price 32 francs.

The syndrome with which the author is concerned affects the extremities and consists in cyanosis, coldness, sweating and subcutaneous thickening. It is a painless and unvarying condition, not leading to gangrene, blistering or "deadness" of the extremities, and is thus seen to differ from Raynaud's disease and thrombo-angeitis obliterans. Allied, but differing conditions are Raynaud's disease, erythromelalgia, scleroderma, recurring phlyctenulosis, various œdemas and urticaria. Associated symptoms are sometimes found, such as sensory impairment of the affected regions and local muscular atrophy.

The condition is commonly found in association with hereditary vasomotor instability, and sometimes in tuberculous subjects and in the subjects of hereditary syphilis.

The author regards disorders of endocrine function as primarily responsible, but there appears to be no information as to which gland is most concerned or the nature of its dysfunction. There is, in other words, the usual vagueness which characterizes hypotheses invoking endocrine disorders. The immediate cause of the condition is capillary stasis from defective sympathetic nervous activity. With etiological and pathological knowledge so vague and speculative, it follows that indications for treatment are also of a somewhat unconvincing character.

Études sur les Maladies familiales nerveuses et dystrophiques. By O. Crouzon. Paris: Masson et Cie. 1929. Pp. 382. Price 55 francs.

This volume is an elaboration of Dr. Crouzon's valuable article on the subject contributed to the "Traité de Pathologie médicale et de Thérapeutique appliquée." Part I is concerned with the familial affections of a strictly neurological order, and the clinical features of a very large number of syndromes—rare and common—are ably set out. Two or three conditions are included as "nervous disorders, exceptionally familial," amongst which one is surprised to see von Recklinghausen's disease. The second part deals with dystrophic familial affections, which include cranio-facial dysostosis, cleido-cranial dysostosis, familial pleonosteosis, and heredity osteopathy. Dr. Crouzon's book is valuable for the purpose of reference, and he has dealt with a great number of obscure and transitional cases which have appeared sporadically in the literature.

The encyclopædic value of this monograph is very seriously vitiated, however, by the lack of a proper bibliography, a feature which is essential in a work of this character.

The Mechanism of the Larynx. By V. E. Negus. Pp. 528. London Wm. Heinemann, Ltd. 1929. Price 45s.

In this exhaustive monograph, the author has dealt with the embryology, the comparative morphology and the physiology of the larynx. The subject matter is almost entirely original, although the work of other investigators in this field is fully discussed and incorporated. He emphasizes that speech is not the only activity of the larynx, nor even one of its more important functions. He traces the structural alterations in the complexity of the larynx which have evolved to meet the habits and needs of the species, and the modifications in its anatomy brought about by the functions of olfaction, respiration and deglutition, and the development of prehensile forelimbs. Finally, the author leads up to the problem of the employment of sound as a means of communication amongst the animal creation, and thence to the function of the larynx as an instrument of phonation.

The Autonomic Nervous System. By ALBERT KUNTZ. Pp. 569. London: Baillière, Tindall and Cox. Price 31s. 6d.

There is a rapidly growing interest in the problems attendant upon the study of the sympathetic and parasympathetic nervous systems, as illustrated by the quantity of research at present carried out on their anatomy and physiology.

Unfortunately there are few comprehensive monographs which are in accord with modern conceptions. Dr. Kuntz's book, therefore, fills a very real want. The plan of this monograph comprises first an anatomical and histological discussion of the autonomic nervous system; the general physiology is next dealt with, and he afterwards deals with special physiological details as the innervation of the heart, blood-vessels, the respiratory, alimentary and biliary systems, the internal and external secretory glands, the uro-genital apparatus, the eye and the striped muscles. Two chapters are devoted to general and special pathology. There is a useful discussion on the mechanism of visceral pain, and the conception of Eppinger and Hess of vagotonia and sympatheticotonia is critically discussed, and is regarded as a useful working hypothesis. A section on the surgery of the autonomic system concludes the volume. There is an excellent bibliography to each chapter, and each section is concluded with a judicial exposition of the various problems which have been dealt with in the text. A chapter on the methods of investigation of the sympathetic nervous system, as practicable to the clinician, would have been useful.

La Maladie de Friedreich. By P. MOLLARET. Pp. 308. Paris: Amédée Legrand. 1929.

This volume represents the most complete monograph available on the clinical aspects of Friedreich's ataxia. The author does not deal at all with the pathology of the disease. Each of the classical signs and symptoms is treated exhaustively with frequent reference to the author's personal series of 21 cases. Among the rarer clinical features which are studied may be mentioned affections of the auditory nerve, strabismus, optic atrophy, visual complications, psychical changes, hepatic efficiency, and abnormalities in the spinal fluid. A useful section is given on the course of the disease, the frequency of remissions and the mode of dying of these patients. Atypical cases are considered under the following four groups: (1) Forms with muscle atrophy; (2) the *formes frustes*; (3) transition types linking classical cases of Friedreich's ataxia with Marie's ataxia on the one hand, and familial spastic paraplegia on the other; and (4) cases in association with other neurological syndromes, in particular myopathy, idiocy, Huntington's chorea and hysteria.

An excellent bibliography concludes this monograph. Dr. Mollaret's book is valuable as a work for reference, but a detailed and voluminous monograph on what is after all an artificial pigeon-hole for the great group of familial ataxias is out of accord with the modern conceptions of neurology. What is required

is a broadminded effort to collect and study the classical subtypes of this group as a whole rather than a segregation and study of individual cases in rigid walled compartments.

Études cliniques sur les Syndromes moteurs et Réflexes de la Paroi abdominale et d'Origine cérébrale. Par AKE BARKMAN. S. 302. Upsala: Almquist and Wiksells.

In a long historical introduction the author attempts to show that in the evolution of our conceptions of localization in the fore-brain it has been the clinician rather than the experimental physiologist or anatomist who has first perceived the truth; and that the current conceptions concerning the cerebral representation of the muscular activity of the abdominal wall are completely at variance with the conclusions which he sets forth in this volume.

In Part II he reviews briefly the anatomy and individual action of the abdominal muscles, and then presents in some detail his methods of investigation and the results of his examination of 135 normal adults. In Part III are given the analyses of the findings in 65 cases of cortical, subcortical, or capsular lesions of the pyramidal tracts. The author concludes that in cerebral hemiplegia the abdominal muscles are involved constantly and permanently. This hemiparesis is best observed by the deviation of the umbilicus and arching of the mid-line to the normal side during performance of the test movements, especially by forcible retraction of the abdomen. It was frequently observed even when the abdominal reflexes were symmetrical, or obtainable on neither side. It was demonstrable by these methods in a few patients in whom all other signs of a pre-existing hemiplegia had completely cleared up.

The author concludes that there is cortical representation of the movements of the abdominal wall, and that this representation is further subdivided into at least two centres, one for the upper and one for the lower quadrant. He believes that the essential region must lie precisely between the centres for the hip and shoulder.

L'Hyperostose frontale interne: Syndrome de l'Hyperostose frontale interne avec Adipose et Troubles cérébraux. Par F. MOREL. Pp. 95 avec 13 figures Paris: G. Doin. 1929. Price 20 francs.

The extreme but irregular thickening of the inner surface of the frontal bone which is occasionally visible in radiographs of the skull is fully and carefully described in this small monograph. It is generally found in advanced age, and seems to be commoner in women than in men. It is usually a chance radiographic or pathological finding, but it is not infrequently associated with clinical symptoms, as adiposity, disturbances of sleep, polyphagia, polydipsia, general asthenia, severe headaches and sometimes senile epilepsy. There is evidence that it is related to disturbances in the infundibulo-tuberian region, and that the essential factor in its pathogenesis is a disturbance in the calcium

metabolism. Its localization is explained by the tension of the dura mater on the frontal bone.

This volume is well illustrated by radiographs, and the literature on the subject from the days of Morgagni is fully reviewed.

Handbuch der Geisteskrankheiten. Herausgegeben von OSWALD BUMKE. Siebenter Band. Spezieller Teil III. S. 700 mit 74 Abbildungen. Berlin: Springer. 1928. Price 66 Marks.

The study of the exogenous reaction-types and the organic psychoses has been so much influenced by the work of Bonhoeffer that the present volume, which deals with these conditions, may be regarded as a monument to him. In an excellent introductory essay Stertz points out how Bonhoeffer's examination of the symptomatic psychoses led to his description of the now familiar "exogenous types of predilection," and later to his disputable hypothesis of intermediary factors (ätiologische Zwischenglieder), secondary to metabolic changes. The extension of Bonhoeffer's findings to the organic psychoses, which are really "exogenous disorders that have become chronic," is discussed at some length: in these, it is concluded, dementia is the "axial syndrome" and the familiar exogenous types are "peripheral." Stertz puts forward his view that Bonhoeffer's various exogenous types of reaction are not of equal diagnostic value and can be classified as including obligatory or fundamental symptoms, and facultative or accessory symptoms, dependent for their appearance on various conditions and likely to occur also in endogenous disorders. The influence of factors such as premorbid personality, age and constitution generally, is discussed, as well as the extent to which mental disorders of endocrine origin conform to the exogenous type of reaction. In the endogenous dementing processes, epileptic and schizophrenic, the same principles as in the "organic" disorders are held to apply.

Ewald gives an exhaustive clinical account of the exogenous forms of reaction, classified as delirious disorders, twilight states, "amentia," hallucinatory forms, and then the post-psychotic conditions. He next describes in detail the mental changes seen in individual disorders of the thoracic and abdominal organs, the blood, the ductless glands, &c., as well as in the infectious diseases, with a brief appendix on the generative psychoses of women, in which the psychological factors are too little considered. Ewald agrees with Bonhoeffer that there is little hope of being able to recognize the ætiology of symptomatic psychoses solely from a study, however careful, of their form; for this the somatic accompaniments will be much more valuable.

Psychoses due chiefly to exogenous toxic substances are dealt with by Meggendorfer. These psychoses, he holds, must be regarded as the product of a biological interaction between the poison and the poisoned organism. The implications of this are gone into thoroughly; then the various poisons are taken in order, alcohol and morphia being dealt with very faithfully, as might be expected in view of their importance. Industrial poisons also receive adequate consideration.

Mental changes following injury to the brain are described by B. Pfeifer, who also writes on psychoses associated with meningitis and cerebral tumour. The common belief that "Witzelsucht" is characteristic of tumours of the frontal lobe is incidentally laid by the heels.

The section by W. Runge on psychoses in other disorders of the brain than those just referred to, contains a thorough exposition of the psychic changes in encephalitis lethargica. Disseminated sclerosis, Schilder's encephalitis, extrapyramidal disorders, abscess, hæmorrhage and softening are considered also. These sections consist largely of useful summarizations of the literature, reliable but tedious.

Throughout the book prognosis and treatment are not neglected; the sections on drug addiction are particularly informative in this connection.

Das Schizophrene Denken. Von JAKOB FROSTIG. S. 187. Leipzig: G. Thieme. 1929. Price M. 4.

The subtitle of this book indicates that it is an attempt to study the "nonsensical" utterances of the schizophrenic from a phenomenological standpoint. The phenomenology which the author means, however, is that of Husserl, rather than of Jaspers; the work is consequently philosophical, not clinical, and seems hardly likely to be of interest to English psychiatrists.

The discussion, though severely abstract and theoretical, is not obscure. It is, however, such as scarcely to lend itself to brief exposition. The author's main conclusion is that whereas for normal people words serve to "signalize collective structures" (the essential features through which we experience objects as being), for the schizophrenic this is no longer the case; there is in him a general inability to actualize collective structures and the elements of consciousness which appertain to these structures.

Die psychischen Reaktionsformen. Von HARRY MARCUSE. S. 262. Berlin: S. Karger. 1929. Price M. 22.

This work is an expansion of the author's previous contributions to an "energetic theory of the psychoses." His theoretical views, which bulk largely, are based on the psychological teachings of Jodl.

Mental happenings are for him reactions to stimuli, divisible into primary and secondary, according as the stimuli are "presentative" and actual, or past and now reproduced, leading to ideas. In addition to the stimulus, the "psychic constitution" is recognized as important, i.e., the manner of reacting to stimuli, and the distinguishing feature here is said to be the "intensity" of the psychic activity. Constitutions are classified accordingly. The author holds that there is one somatogenic psychosis which includes schizophrenia, paranoia and manic-depressive insanity, the ætiological agent being a hypothetical "catatonic noxa," the reaction to which depends on the mental constitution of the affected person. Hypnosis is given as a valued means of

differentiating psychogenic from somatogenic reactions and of treating the former. Chapters on simulation, dreams and general cultural questions complete this ingenious but unconvincing attempt to rearrange the psychoses on the basis of a psychological theory.

Die Psychologie der Schizophrenen. Von CARL SCHNEIDER. S. 301. Leipzig: Georg Thieme. 1930. Price M. 25.

The author's views on schizophrenia are here set forth more fully and consecutively than in his earlier papers, which have met with a good deal of criticism. The present work has profited from this, and provides a useful exposition of the problems of schizophrenia as well as a stimulating attempt at their solution. There is no concealment of the difficulties and gaps in this: it is not even maintained that psychopathological investigation establishes schizophrenia as a "disease-unity," but the author has more or less accepted the current clinical conception of the disorder and confined himself to clarifying its psychopathology.

In the beginning he considers the frequency with which the most important schizophrenic symptoms were met with in 408 carefully observed cases of his own. He then gives an excellent critical review of the present views on schizophrenia, and considers the relationship between the symptoms of this disorder and the experience of falling asleep. The similarity, which had previously been pointed out by Kraepelin and Bumke, is considerable and provides the starting point for the development of the author's views. He examines the various common symptoms, "primary" and "accessory," and concludes that other features than these are the true characteristics of the psychic life and expression of the schizophrenic. Bodily changes he disposes of as nosologically unimportant; search after causes is equally useless from this point of view. He is equally critical of the studies in physique and personality so far as they bear on this problem. He concludes with a brief but valuable section, on the course, prognosis, delimination, diagnosis in the individual case, and treatment of the disorder.

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EDITOR.